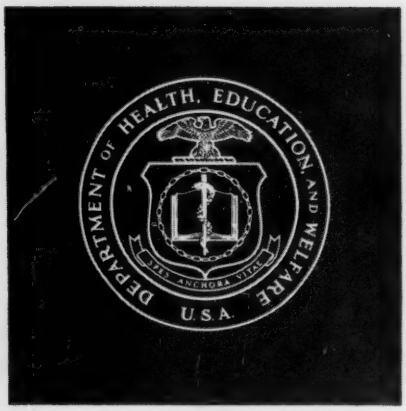
Psychopharmacology Service Center Bulletin



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A Few Kind Words for the Clinical Psychopharmacologist

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As Roger Russell recently pointed out in these pages,[1] we should like to have some rationale for selecting psychotherapeutic drugs based on their effect on model behaviors. Unfortunately, instances in the history of pharmacology in which drugs were introduced into therapy on rational bases are comparatively rare. In fact, the procedure has generally been reversed with psychotherapeutic drugs. A drug class is first found to be therapeutic, and then a rational basis for its action is sought in a battery of behavioral, biochemical, or physiological tests.

The situation regarding the selection of drugs is not hopeless, as evidenced by the host of new compounds presented for clinical trial on the basis of pharmacological studies. Many criteria have been used for such preclinical screening: alteration of avoidance or other operant-conditioned behavior; frank sedation, analgesia, or anesthesia; change in spontaneous motor activity; antagonism of the effects of amphetamine or reserpine; production of catalepsy; anticonvulsant effects on electrically- or chemically-induced seizures; anti-cholinergic, -adrenergic, -serotonin, or -histamine effects; internuncial neuronal block; as well as many others. To date, no single group of these pharmacological tests has been found which infallibly selects a clinically effective agent. Again, it should be pointed out that most of these screening tests were developed *after* therapeutically effective compounds had been discovered, when clinically active compounds demonstrated these actions.

What I am leading up to is this: Historically, advances in psychopharmacology have been made almost exclusively through empirical, naturalistic, or clinical observations, and despite the recent infusion of more refined scientific method, it would seem that new treatments in the near future might continue to arise in this way. Brash as it may sound, a major goal for the clinical psychopharmacologist should be developing hypotheses about drug-mind relationships and testing them in clinical trials. From the prehistoric time when some genius noted the curious effect on the senses of drinking juices from fermented plants to the incidental clinical observations of the unique sedative effects of chlorpromazine and reserpine, observers of human behavior have made the major contributions to this field. Clinical hunches (hypotheses, if you will) have advanced other psychiatric treatment as well. The proposal of a large unconscious mental life was such a hunch. So was the possible antagonism between seizures and schizophrenia, which, even though probably wrong, was productive of electroconvulsive therapy. Malaria therapy for paresis evolved from the observation that the disease was ameliorated in those patients who managed to survive typhus fever. As in all fields of science, big discoveries come more from relating facts than from finding them. In psychiatry, the clinician is still best qualified for such a function.

I submit that the job of the clinical psychopharmacologist should entail more than simply taking an endless series of new compounds enthusiastically pressed upon him by pharmaceutical firms to find out, one way or another, what they do to patients. He should be given encouragement to apply his imagination and occasionally play the long-shot hunch. To be sure, patients' welfare cannot be compromised, and such studies should be conducted with an ever-present regard for ethical and humanitarian considerations. Unfortunately, the legal perils of clinical investigation tend to hobble any really new approaches to treatment, forcing clinicians more and more into the "drug-tester" role, which is safer but duller.

Few persons are ever going to discover an important new treatment. Much of the job of the clinical psychopharmacologist will be the more pedestrian but nonetheless important work of studying new drugs which appear promising on the basis of existing preclinical screening techniques. This operation can be divided into five sequential stages: (*a*) preliminary human pharmacology; (*b*) preliminary determinations of therapeutic indications and efficacy, doses, side effects, and toxicity; (*c*) controlled comparison with other drugs or treatments; (*d*) elucidation of the role of the drug in the total treatment program; and (*e*) search for clinical clues for a rational therapy.

With each of these succeeding steps, finer scientific methods can be introduced into the program, but I think it should be emphasized at the outset that all stages are important and should be thought of as having equal status.

PRELIMINARY HUMAN PHARMACOLOGY

Ethical and legal restraints in the United States discourage many investigators from working in this area. Pharmaceutical companies all complain of the shortage of investigators willing to study the earliest human pharmacology of new compounds. The work is risky, requires scrupulous clinical and laboratory observation, but is not very rewarding scientifically. The usual goal is to establish a dose-response curve and test for toxicity. Many studies are done in prisoners, often under less than ideal circumstances. To improve the conditions under

[1] Russell, Roger W. An approach to the development of animal screening techniques in psychopharmacology. *Psychopharmacology Service Center Bulletin,* December 1960, pp. 1–7. (National Institute of Mental Health, Bethesda 14, Md.)

which these studies are done and increase incentives for doing them will require both financial support and scientific recognition. An integrated program might be desirable, supported either by private industry, the Government, or both.

So far, this problem begs solution. Although prisoners are most often used for such studies, their "normality" and the extent of their "voluntary" participation is frequently questioned. Of course, normal volunteers may be poor subjects for evaluating effects of psychotherapeutic drugs; responses to chlorpromazine and reserpine in normals differ in many respects from those of psychotics. Using psychotic patients for very early drug studies creates ethical problems as they are seldom able to give a valid consent. Assuming one could find satisfactory subjects in adequate numbers, augmented staffs would still be required for the obligatory close clinical and laboratory controls. Progress at this level of drug exploration will come only with increased public acceptance and support for use of selected human subjects, based on the potential benefits for many.

PRELIMINARY ASSESSMENT OF THERAPEUTIC INDICATIONS, DOSES, EFFICACY, AND SIDE EFFECTS

The usual practice at this stage is to treat patients with the drug and see what happens. Done by a skilled clinician, this method has much to recommend it. The early papers on chlorpromazine and reserpine, reporting the use of essentially this technique, have stood the test of time well. It is essential that the drug be used in a broad spectrum of disorders and in a fairly wide dose range. Oddly enough, the sicker the patients or the more potent the drug, the easier screening is at this stage. Evaluating a new drug in schizophrenia is generally easier than in less severe or self-limiting illnesses such as psychoneurosis or depression. If nothing else, this method provides a rapid source of many opinions of a new agent from which some consensus may be reached.

Empirical methods such as this are considered disreputable by some because evaluations may be wrong or unduly enthusiastic. Lacking certain safeguards to be mentioned below, the technique is subject to error even when practiced by experts. However, there are two kinds of error. In my opinion, the error of undue initial enthusiasm for chlorpromazine or reserpine was far less serious than the error of disregarding or rejecting these new treatments would have been. Then, too, the truth will out. One can call to mind a number of drugs erroneously reported as efficacious which are seldom used today.

Despite extensive animal and preliminary human toxicity studies, the clinician can be virtually certain of encountering unexpected troubles. For detecting possible side effects, large batteries of laboratory tests are far less valuable than close clinical observation. Major complications of most psychotherapeutic agents have first become apparent in man: agranulocytosis and jaundice from phenothiazines, extrapyramidal syndromes from rauwolfia alkaloids and phenothiazines, anaphylactoid reactions from meprobamate, jaundice from iproniazid, and so on. Sometimes a side effect is a function of dose, in which case it may be uncovered by the clinician using intensive therapy; examples are seizures from phenothiazines or pigmentary retinopathy from thioridazine. Study of side effects and complications is inevitably part of clinical screening at this stage.

CONTROLLED COMPARISON WITH OTHER DRUGS OR TREATMENTS

Once one has a good idea of a drug's indications, doses, and side effects, one can plan a controlled study—*and not before*. Otherwise, one risks wasted effort, error, or intolerable hazards to patients. Having this information, one can apply the techniques of controlled therapeutic experiment: large sample size, random assignment of treatments, objective methods of evaluation, blind controls, and statistical analysis of data.

Size of the sample required will depend on the difficulty of the questions asked. Forty cases were enough to show us clear differences between chlorpromazine and a placebo in early studies. Later, in the Veterans Administration Cooperative Studies of Chemotherapy in Psychiatry, it took more than 100 patients in each treatment group to show the differences between chlorpromazine and promazine or mepazine, while no differences were shown between chlorpromazine and three other drugs (prochlorperazine, perphenazine, and triflupromazine). Hopefully, improvements in rating devices and statistical techniques may improve differentiation of drugs.

A placebo control should probably be employed if the illness studied is variable or self-limiting (for example, depressions) or if the drug is of questionable therapeutic value. Preliminary clinical screening techniques mentioned above are probably adequate to eliminate most ineffective drugs. If the drug has some demonstrated therapeutic efficacy, a more rewarding question to ask is whether it is as good as, better than, or worse than some other drug of proven efficacy for the illness being treated. Use of either a comparison drug or a placebo implies concurrent double-blind control, with neither patients nor raters knowing the identity of medications being given.

Attempts to gain too much precision may be useless. Clear distinction exists between statistical and clinical significance, though it is frequently overlooked. Not long ago, I reviewed a paper in which one mean score for a treated group was about 40 and for another 43, the p value of the difference in means being less than .001. Impressed by the p value, the authors stated that

in this particular respect there was a "great difference" between the groups. I felt obliged to point out that regardless of whether the scale had 45 or 500 points (it was never stated), the difference probably didn't amount to much clinically. Even if it is possible to demonstrate statistically significant differences between two treatments with great numbers of cases, the achievement might have dubious clinical value. Much effort could be wasted in straining at such gnats rather than adequately testing a large number of drugs for simple therapeutic efficacy.

One scarcely dares these days to categorize patients by several degrees of improvement (or lack of it) in a drug trial. Rather, it is more fashionable to use any one of many rating scales, comparing mean scores of each treatment group. A drug which caused considerable improvement in 5 per cent of the patients might by this technique look worse than one causing minimal improvement in 50 per cent of the patients, yet the former could be the more important result. Group averages tend to blur individual responses, which are far more meaningful to clinicians (and patients, too). I recently reviewed another paper in which the writer (unconsciously, I suppose) stated in one part of the paper that differences between treatment groups were highly significant statistically, and in another part that none of the patients in either group improved enough to leave the hospital or be considered for discharge. We must constantly strive to make studies in this stage of drug screening as clinically meaningful as possible.

ROLE OF THE DRUG IN THE TOTAL TREATMENT PROGRAM

Simply demonstrating therapeutic efficacy of a drug, no matter how elegant the method, is not the end of the clinical psychopharmacologists' work. We need to know a lot more about the drug. How does it compare with other treatments: individual or group psychotherapy, milieu therapy, electroconvulsive therapy? How does it work in combination with each of these therapies? Are any advantages to be gained by combining it with other drugs of therapeutic value? Why does it fail to work in some patients? What effect does the general hospital setting have on the results obtained? Or even the attitudes of individual physicians? Can one predict which drug is best for which patient? What is a proper maintenance program? How can patients be managed on drugs out of the hospital? How can drugs be used to prevent re-admission? As yet, this stage of clinical psychopharmacology is just really getting started.

SEARCH FOR CLINICAL CLUES FOR A RATIONAL THERAPY

Fortunately, throughout medical history we have been able to use treatments effectively without understanding them. However, there is a powerful incentive to try to understand the rationale of drug therapy. As one uses these drugs, certain clinical phenomena raise speculations about their mode of action. Is the extrapyramidal syndrome a clinical curiosity, or does it have an important bearing on the effectiveness of drugs in schizophrenia? Is it just fortuitous that such drugs also affect the autonomic nervous system, albeit in often diverse ways? Can one still detect a common thread of "sedation" in all effective tranquilizers? Does the excitement seen during some phases of drug action have a biochemical explanation? What is the significance of electroencephalographic changes induced by drugs? As yet, most of these questions beg answers, but the search for them could be rewarding.

THE CLINICAL PSYCHOPHARMACOLOGIST HIMSELF

The ideal qualifications of a clinical psychopharmacologist would be a synthesis of those of Claude Bernard, Louis Pasteur, and Sigmund Freud. More realistically, one can ask for qualifications possible for many investigators to attain. First, he should have had a rich clinical experience. This means more than simply having worked in the field a long time, implying an intimate acquaintance with patients, hospitals, families, and all the numerous and often capricious factors which may alter the natural history of an emotional illness. Second, he should accept drugs as a treatment and have used other kinds of drugs enough to be aware of the multiple effects drugs may have. Third, he should have at least an intuitive concept of scientific method and principles of logic, and when his own knowledge of these matters is inadequate be willing to consult with those who know more. In the same vein, he should retain a high degree of scientific objectivity. Finally, he must be willing to learn, as a new field advances rapidly.

It is a sad reflection on the past training of physicians that so few know the methods of science, and on the present training of psychiatrists that so few know the use of drugs. Most psychiatrists in this field are men trained in an earlier day when somatic therapies were more important. Some gaps have been filled by the entry into the field of other medical men, usually internists, and clinical psychologists. My own experience leads me to believe that collaboration between psychiatrists, psychologists, and internists in clinical psychopharmacological studies is highly fruitful and that problems in communication diminish with time.

I have been urged to prescribe the best way for clinical psychopharmacological studies to be done, and I am tempted to recommend the way I do, or would like to do, my own studies. I shall not yield to this temptation simply because I'm not sure I know the best way or, indeed, whether there is any single best way. If the

clinical psychopharmacologist brings to his work the qualifications listed here, whatever way he chooses to do his clinical studies will probably be pretty good. Should he also have a large share of the last qualification, the willingness to learn, his way may even become the best.

In this essay, I have emphasized the uniquely important role of the clinical psychopharmacologist in the search for new drug treatments of emotional disorders. The present hierarchical structure of biological sciences assigns decreasing prestige as the size of one's object of study increases. The molecular biologist stands at the pinnacle; those who study the whole man scarcely qualify as scientists. But nowhere is the study of man so vitally important as in the search for drugs which affect the mind.

*The Metabolism of Information in Psychopharmacology**

Investigating the "metabolism" of biomedical information—the generation, digestion, and assimilation of information by the scientific community—is one of the long-term, major projects of the Institute for Advancement of Medical Communication. Tracing the fate of information from its birth in a research laboratory until it is put to practical use, or serves as a basis for further research, is the goal of this investigation. From a better qualitative and quantitative understanding of the processes by which new information is disseminated to nourish both research and medical practice, it is hoped that the efficiency of the biomedical communication system may be improved. For the initial studies[1] in this continuing project, three areas of research—cardiovascular, endocrine, and psychopharmacological—were chosen as examples of rapidly expanding, subject-oriented fields. This brief summary emphasizes the findings relevant to psychopharmacology.

METHODS

Oral reports presented at scientific meetings served as a convenient starting point for tracing the fate of information resulting from research. The annual meeting of the American Heart Association in October 1957 was the source for cardiovascular research reports (275 reports given or "read by title"). The Endocrine Society meeting in June 1958 was used for the field of endocrine research (188 reports). For their respective research fields, these two meetings are the largest and most comprehensive at which results of both basic and clinical research are presented. In the absence of a similar meeting for psychopharmacology, the sample of oral reports for this field was selected somewhat differently. To obtain a complete cross section of psychopharmacological research that had progressed to the point where workers were ready to present their results orally, the programs of national and regional meetings in 1957, at which one might expect reports on psychopharmacological research, were reviewed. The programs of 40 meetings were studied; 151 oral reports from 17 meetings were identified. As an additional check on the completeness of the sample, investigators with grants from the National Institute of Mental Health and other major agencies supporting psychopharmacology, and those working intramurally at the National Institutes of Health or the Veterans Administration, were asked whether they had reported orally in 1957 on their research. An additional 6 reports were identified in this way, bringing the total to 157 oral reports pertaining to psychopharmacology, as this term is defined by the Psychopharmacology Service Center of NIMH.

Questionnaires were sent to the senior authors of all the oral reports in the three subject matter fields to ascertain, among other things, whether and when these reports were submitted to journals and published, and what were the reasons for the sometimes considerable interval between reporting orally and submitting a manuscript for journal publication. To develop answers to the latter question in greater detail, to learn about investigators' experiences with various phases of the communication process, and to explore their attitudes toward some of the problems encountered in disseminating information, 76 of the scientists who returned the questionnaires and 12 nonrespondents were interviewed.

The next step in studying the metabolism of this information was to determine whether and when these same units of information, originally identified as oral reports and later as published papers, appeared in abstracting or indexing services. Some of the objectives of this portion of the study were to determine the coverage of the selected research fields by the major abstracting and/or indexing services, the "overlapping" in coverage among abstracting services, and the average time-lag between primary (journal) and secondary (abstract or index) publication.

Of the 157 questionnaires mailed to psychopharmacology investigators, 110 or 70 per cent were returned, as compared to 61 per cent and 64 per cent of those sent to the cardiovascular and endocrine groups, respectively.

RESULTS AND DISCUSSION

Interval Between Oral Report and Submission of Paper for Publication. The interval between the date of the meeting at which an oral report was presented and the

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[1] These studies were supported in part by Grants MY-3236 from the National Institute of Mental Health, HTS-5414 from the National Heart Institute, and G9429 from the National Science Foundation.

time when the same work was written up and submitted to a journal varied widely. One psychopharmacology paper was submitted to a journal 11 months before it was given at a meeting, whereas in another case submission for publication occurred 25 months after the oral report. The frequency distribution over this range (from −11 to +25 months) was bimodal, with a sharp peak around the time of the meeting and a smaller, less well-defined peak 10 months after the meeting. Similar frequency distribution curves were found for the cardiovascular and endocrine groups of papers, except that a smaller percentage of the papers in the latter two groups were submitted to journals at the time of, or prior to, a meeting than in the psychopharmacology group, where a third of the papers were submitted this early.

Reasons for Delay in Submitting Papers for Publication. Questionnaire respondents chose which of six statements of reasons for delay in submitting a manuscript to a journal after giving an oral report held for them. Most gave multiple answers. In psychopharmacology, by far the most frequently cited reasons were "more pressing work" and "planned to report [this work] as part of a broader paper." The press of other responsibilities was also the most common reason cited by the cardiovascular and endocrine research workers, but the latter groups gave "work not ready to report in final form" as their second most common response in contrast to the psychopharmacology group, where none of the investigators chose this explanation. Another notable difference was that "administrative difficulties" seemed considerably more important to the psychopharmacology group.

In the interviews, authors' attitudes toward writing up a report after giving it orally were explored more fully, since those interviewed could expand on the reasons they cited. For analytic purposes these reasons were classified somewhat differently from those on the questionnaire. Of the 88 interviewees, 10 stated that authors did not delay unduly in preparing manuscripts, whereas another 10 believed that reasons relating to the investigator's personality or personal dynamics were the sole causes for delay. Falling into the category of personal dynamics were such answers as "laziness," "inertia," "prefer to collect data rather than analyze it," and "no interest once experiment is completed." The remainder of the interviewees cited multiple reasons that indicated they felt both personal dynamics and environmental factors, such as "lack of assistance," were important.

Rejection Rates. Only 8 of the psychopharmacology papers were rejected by the first journal to which they were submitted (9 per cent of the 85 papers submitted); 4 of these were resubmitted to a second journal, whereupon 2 were accepted and published, leaving in doubt the ultimate fate of 6 of the 8 papers. This rejection rate for psychopharmacology can be compared with 6 per cent for endocrinology and 9 per cent for cardiology.

Primary Publication. Of those oral reports on which questionnaires were returned, 74 (67 per cent) had been published in a book or journal by June, 1960; the corresponding figure for cardiology was 58 per cent and for endocrinology 62 per cent. Since the time interval from the meeting (or meetings, in the case of psychopharmacology) to the cut-off date was not the same for the three groups (2 years for endocrinology, 2¾ years for cardiology, and an average of 3 years for psychopharmacology), these values for publication "yield" are not exactly comparable.

Publication "Scatter." The published psychopharmacology papers[2] appeared in 50 different journals and 6 books; however, 33 of the journals contained only one paper, and 50 per cent of all the papers were published in 8 journals. The "scatter" for cardiovascular and endocrine papers was considerably less marked.

Journal-Lag. The interval between submission of a manuscript and its publication in a journal averaged 8.4, 6.9, and 7.3 months for psychopharmacology, cardiology, and endocrinology, respectively. The somewhat greater journal lag in psychopharmacology is partly explained by a higher proportion of quarterly journals.

Secondary Publication. Biological Abstracts (BA) abstracted 40 per cent, *Chemical Abstracts* (CA) 26 per cent, *Excerpta Medica* (EM) 35 per cent, and *Psychological Abstracts* (PA) 27 per cent of the psychopharmacology papers. When overlapping coverage, i.e., inclusion of a given paper in more than one abstracting service, was taken into consideration, it was found that 28 per cent of the papers had not been abstracted by any of these four services during the period studied. *Current List of Medical Literature* (CL), now *Index Medicus,* indexed 87 per cent of the psychopharmacology papers. This picture of coverage by abstracting and indexing services is similar in gross detail to that for the cardiovascular and endocrine papers.

BA required an average of 9.4 months, CA 5.2, EM 12.4, PA 14.9, and CL 4.7 months to publish abstracts (or, in the case of CL, index entries) for psychopharmacology papers. Abstracting of psychopharmacology papers by BA, CA, and EM was significantly slower than for cardiovascular or endocrine papers.

Other Findings from the Interviews. Numerous other questions and problems were explored in the interviews. The findings in several areas pointed to special needs and attitudes on the part of workers in psychopharmacological research as compared to workers in other fields. For example, the psychopharmacology group more often emphasized difficulties in finding proper publication outlets, which they attributed to the newness of their field and its interdisciplinary nature, and were more enthusiastic about a hypothetical service from which they could

[2] The number of papers involved here is 110 and includes the 74 mentioned above plus 36 others identified in the course of the study but not used for the previous calculations since they did not result from oral reports given in 1957.

quickly obtain copies of meeting reports and to which they would contribute the text and graphic material from their own oral reports.

CONCLUSIONS

1. Of the factors determining whether and when a given report is published after having been presented orally, the personal characteristics and working conditions of the research worker are probably more important than editorial or other judgments on the quality of the work.

2. For many authors, the time and effort involved in writing a formal paper for publication are important deterrents to sharing with others the results of their work.

3. Within 2 to 3 years—a significant period in rapidly developing fields of research—only 60 to 70 per cent of the information reported at meetings is published and thus made widely and easily available.

4. Delays in publication attributable to journals are commonly cited by research workers; however, author-lag may well be more important.

5. Scatter of papers of related subject matter among different journals is especially marked in psychopharmacology, and it is probable that many workers will not learn of papers pertinent to their work until some time after the papers appear in print—when they have been abstracted or indexed, when they have been cited in another paper, or when colleagues have called attention to them.

6. The field of psychopharmacology appears to be less well served by the standard abstracting services than comparable areas of research.

7. The technique of using oral reports as "tracers" in studying the metabolism of scientific information is valuable and can provide measures of the efficiency of primary and secondary publication in a research field.

*The Reporting and Design of Research on Psychiatric Drug Treatment; A Comparison of Two Years**

This paper reports an attempt to make a broad, quantitative survey of currently published research on psychiatric drug treatment, and to determine, if possible, the trends in recently published research in this area. In particular, we were interested in the kind of information reported in the published studies (the "reporting" aspect) and in how the studies were conducted (the "method" aspect).

The primary basis for our evaluations was the paper entitled "Recommendations for Reporting Studies of Psychiatric Drugs," written by Jonathan O. Cole, Sherman Ross, and Lorraine Bouthilet, and published in *Public Health Reports,* 1957, Vol. 72, pages 638–645. That paper contained the recommendations of a conference devoted specifically to methods of conducting and reporting psychiatric drug research. It seemed to us that the publication of such a report, combined with an apparent general increase in attention to drug research, would improve the quality of the literature in this field. Additionally, we had the impression that adherence to certain significant features of research design would be associated with superior quality in both the reporting and design of psychopharmacological research.

The years selected for analysis were fiscal year 1957, which immediately preceded publication of the paper by Cole et al., and fiscal year 1960, the most recent complete year available. It was felt that enough time had elapsed between 1957 and 1960 to permit measurable improvements to occur.

With these considerations in mind, we examined the data with reference to the following hypotheses:

1. That the reporting would be more complete for studies published in 1960 than for those published in 1957.

2. That more precise methodology would have been used in the studies published in 1960 than for those published in 1957.

3. That the reporting would be more complete and the methodology more precise in both years for studies which had used any one of the following: (*a*) double-blind techniques, (*b*) a control group or a control interval, and (*c*) specified criteria for evaluating change.

METHOD

All issues (excluding special supplements) of the following journals were surveyed for the years indicated: *American Journal of Psychiatry* (1957 and 1960); *A.M.A. Archives of Neurology and Psychiatry* (1957, not published in 1960); *A.M.A. Archives of General Psychiatry* (1960, not published in 1957); *Diseases of the Nervous System* (1957 and 1960); *Journal of Clinical and Experimental Psy-*

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This paper was presented at the Sixth Annual Conference, Veterans Administration Cooperative Chemotherapy Studies in Psychiatry and Broad Research Approaches to Mental Illness, held in Cincinnati, Ohio, March 27–29, 1961, and will be published later this year in the Transactions of the Conference. It is included here by special permission from the Veterans Administration.

chopathology (1957 and 1960); *Journal of Nervous and Mental Disease* (1957 and 1960); and the *Psychiatric Quarterly* (1957 and 1960).

From these journals, all articles were selected which met the following criteria: (*a*) primarily concerned with the effects of drug treatment, (*b*) not designated a "clinical note," (*c*) not reporting in one article two or more methodologically dissimilar studies, and (*d*) reporting the use of one of the drugs included in a previously prepared list of 35 common and experimental tranquilizing or energizing "psychiatric" drugs, excluding narcotics and barbiturates.

A check list[1] incorporating most of the recommendations given in the paper by Cole et al. was used for rating the reporting and methodological quality of the selected studies. In its final form, the check list included 28 items on reporting and 7 items on the design or methodological aspect of evaluating change. The items on reporting covered treatment setting, selection and description of patients, drug administration (including toxicity reactions), and evaluation of change. A sample of one page of the check list is shown in Figure 1, and the check list items, excluding treatment setting, are shown in Figures 2, 3, and 4.

Each article was read and scored on the 35 items of the check list. Most of the items were scored as "not specified," "generally specified," or "clearly specified," but 10 were scored on a two-point present-absent scale. Definitions and scoring rules for distinguishing between rating categories were drawn up in advance. For example, in scoring the age range of patients, a range of more than 20 years was "general"; a range of 20 years or less was "specific," as was any range if a statement of central tendency (e.g., a mean) was given. By and large, we tried to be lenient in requirements for a "specific" rating. Using these rules, the agreement between the two raters on "specific" and "present" versus "general," "not specified," and "absent" was 0.88 in a 10 per cent random sample of articles.

Title of article:
Authors:
Journal:
Drugs:

I. Setting	NS	G	S
II. Subject Variables			
1. Sample size	NS	G	S
2. Age	NS	G	S
3. Sex	NS	G	S
4. Duration of illness	NS	G	S
5. Onset	NS	G	S
6. Duration of hospitalization	NS	G	S
7. Diagnoses	NS	G	S
8. Organic disease	NS	G	S
9. Mental status	NS	G	S

FIGURE 1: *Sample of Page 1 of Check List for Survey of Drug Study Literature.*

[1] The complete check list and the definitions and scoring rules are available from the authors.

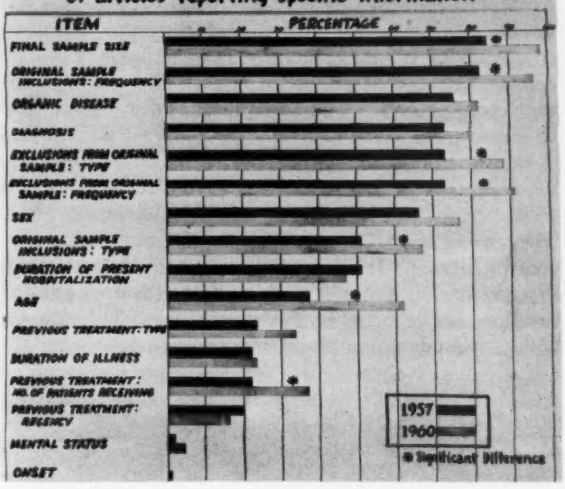
RESULTS

There were 45 articles in fiscal year 1957 that met the selection criteria and 61 in fiscal year 1960, an increase of 36 per cent.

The results in terms of individual check list items are shown in Figures 2, 3, and 4. Each figure shows for each year the percentage of "specific" or "present" ratings[2] for a group of items dealing with a single aspect of the report or with the design of psychiatric drug research. Within each figure, items are ordered according to their prevalence in 1957. Statistically significant percentage differences are asterisked.[3] Treatment setting, the single item in its category, is not shown. It was specifically reported in 6.7 per cent of the 1957 papers and 1.6 per cent of the 1960 papers, a decrease of 5.1 per cent (not significant).

Several features of the figures are of special interest. First, despite the large number of significant differences, chance alone would account for the occurrence of some,

Fig. 2 Selection and Description of Patients: Percent of articles reporting specific information



[2] The data presented here are concerned only with "specific" or "present" ratings. Examination of the data revealed a rank-order correlation of 1.00 for present-absent, 0.70 for specific vs. not specific for 1957, and 0.63 for specific vs. not specific for 1960, indicating that consideration of the "general" rating category would add little information.

[3] The hypotheses of this study predicted improvement and so dictated one-tailed statistical tests. Complete statistical rigor would demand accepting the null hypothesis and concluding "no increase established" rather than "difference established in the wrong direction" for all decrements, however large. Since we hope that this report will be stimulative rather than conclusive, however, two-tailed probabilities are reported for all decrements that would have been significant if the hypothesis had specified mere change rather than improvement.

For the comparison of differences in individual items, a probability level of .10 was accepted as significant in order to avoid discarding some valuable difference. Elsewhere in the report, a probability level of .05 was adopted as significant.

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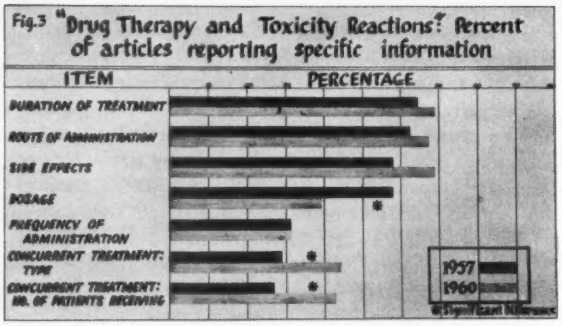
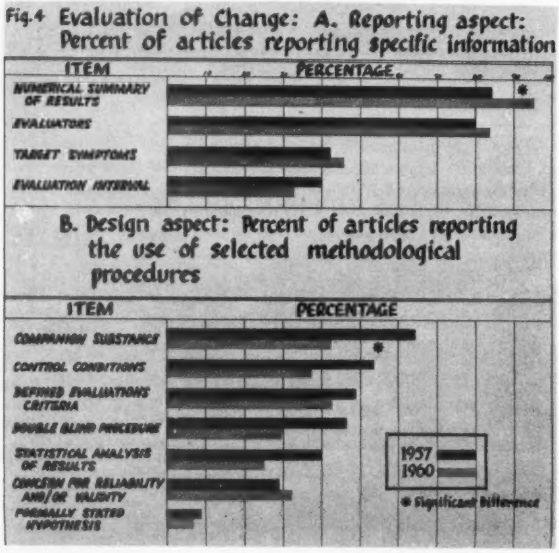


making it unwise to select any one item for specific attention. A number of the "reporting" items (Figures 2, 3, and 4a) occur only rarely in the literature, although all the check list items are identified by the 1957 conference as desirable for inclusion in reports of psychiatric drug research. Also, there seems to be a general tendency for reporting items to be more prevalent in 1960 than in 1957, an initial suggestion of support for the first hypothesis. Furthermore, one can distinguish one homogeneous cluster of items which occur relatively frequently in 1957 and increase rather markedly in percentage in 1960. Those items are the ones dealing with the reporting of types and frequencies of inclusions and exclusions, or, more generally, with the determination of sample size. Another group, the items reporting previous or concurrent treatment, is characterized by low 1957 percentages which tend toward increase in 1960. They are of special interest in their role as experimental control factors. It is interesting to note that not only those items, but also others which deal with drug administration, are reported in this area of medical literature with only moderate or lower frequencies.



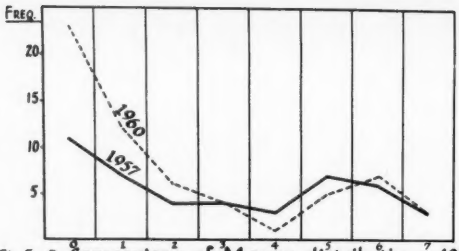
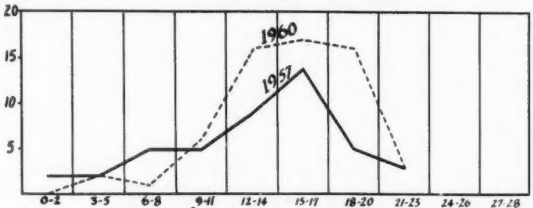


Fig.5 a. Comparison of M score distributions - 1957 & 1960



b. Comparison of R score distributions-1957 & 1960

Figure 4b, which reports the use of methodological features commonly accepted in psychopharmacological research, warrants especially close attention. Average prevalence of these items is clearly less than for the reporting items, and there is a slight, although insignificant, trend (two-tailed binomial probability, .12) toward decreasing occurrence. Some caution is necessary in interpreting these figures. Because of the 36 per cent increase in the number of articles published in 1960 over 1957, percentage increases represent an increase in the absolute number of articles involved, whereas a decrease may occur where there is no appreciable change in the number of articles. The lower percentage of occurrence of methodological features is a case in point; the absolute frequencies involved are relatively constant from 1957 to 1960. Nevertheless, it is clear that the second hypothesis is not supported. The use of standard methodological procedures is not increasing.

Two scales were derived from the check list for use in organizing the check list data. The 35 basic items on the list were assigned to one or the other of the two scales depending on whether they reflected reporting quality (treatment setting plus the items shown in Figures 2, 3, and 4a) or indicated the use of some generally accepted research design feature (items shown in Figure

TABLE 1.—*Comparison of R and M Scores for 1957 and 1960*

Scale	1957		1960		Mean Diff.
	Mean Score	S.D.	Mean Score	S.D.	
R	13.3	5.1	15.1	4.3	1.8*
M	2.9	2.4	2.2	2.4	−0.7

*Significant at .05 level.

TABLE 2.—*Comparison of VA and Non-VA Research*

Scale	Year	VA			Non-VA			Mean Diff.
		N	Mean Score	S.D.	N	Mean Score	S.D.	
R	1957	7	14.9	5.6	38	13.0	5.1	1.9
	1960	5	16.4	1.1	56	14.9	4.4	1.5
M	1957	7	5.0	1.4	38	2.5	2.4	2.5*
	1960	5	5.2	3.0	56	1.9	2.2	3.3*

*Significant at .02 level; other values, $p > .05$.

4b). Each article was given an "R score" by counting one point for each reporting item evaluated as "clearly specified." An "M score" was similarly assigned by counting one point for each methodological feature evaluated as present. Thus, an R score (possible range, 0–28) reflects the amount of specific information reported, and an M score (possible range, 0–7) the number of well accepted methodological features utilized in the work. The means and standard deviations of the M and R scores for 1957 and 1960 are shown in Table 1. As predicted by the first hypothesis, there is a statistically significant increase in mean R score from 1957 to 1960. The comparable mean increase in M score predicted by the second hypothesis is not found.

Inspection of the frequency distribution of M and R scores is helpful (Figure 5). It is evident that the mean and standard deviation are not appropriate descriptive statistics for the skewed, bimodal distribution of M scores. Tested by a more appropriate statistic, the Mann-Whitney U, the M score decrease is shown to approach significance (two-tailed probability, .09). The M score distribution,

TABLE 3.—*Comparison of M Scores for Selected Items*

Item	Item Present			Item Absent			Mean Diff.**
	N	Mean M Score*	S.D.	N	Mean M Score*	S.D.	
	1957						
Double blind	21	4.2	1.2	24	0.9	1.1	3.3
Control conditions	24	3.8	1.7	21	0.9	1.4	2.9
Defined criteria	22	3.7	2.1	23	1.3	1.6	2.4
	1960						
Double blind	18	4.4	1.2	43	0.8	1.0	3.6
Control conditions	23	3.8	1.7	38	0.6	0.8	3.2
Defined criteria	26	3.0	2.3	35	0.8	1.2	2.2

* Corrected for presence of variable.
** All values significant beyond the .001 level.

TABLE 4.—*Comparison of R Scores for Selected Items*

Item	Item Present			Item Absent			Mean Diff.
	N	Mean R Score	S.D.	N	Mean R Score	S.D.	
	1957						
Double blind	21	15.5	4.5	24	11.4	4.8	*4.1
Control conditions	24	14.4	5.0	21	12.1	5.0	*2.3
Defined criteria	22	15.2	3.5	23	11.5	5.8	3.7
	1960						
Double blind	18	17.2	3.3	43	14.2	4.3	*3.0
Control conditions	23	16.6	3.2	38	14.1	4.6	2.5
Defined criteria	26	15.5	3.2	35	14.7	5.0	*0.8

*Significant at .01 level; other values $p > .05$.

however, does show that the large increase in number of publications in 1960 occurs at the lower end of the scale, among studies using none or only one of the methodological features tallied. Quite clearly, the second hypothesis is not supported; the data, in fact, give some evidence in favor of the opposite conclusion, i.e., that there is a decrease in methodological quality, although not reliably so.

On the other hand, the increase in the distribution of R scores is around the mode of the 1957 distribution. Although there is a statistically significant increase in mean R score, it does not appear as a clear-cut shift of the entire distribution in a favorable direction. In other words, the mean increase in reporting scores is attributable to an increase in the number of articles of only moderate reporting quality and a relative decrease in the amount of very poorly reported literature. The most typical articles seem to contain about as much information in 1960 as in 1957, and much of the information considered desirable for such articles is still commonly omitted.

Table 2 presents a comparison of articles originating in Veterans Administration settings with the rest of the literature. All of the mean differences are favorable to the VA work, and the differences in M scores are significant for both years. These latter differences are impressively great: the methodological quality of VA research is clearly superior.

The third hypothesis predicted that three methodological features, the double-blind technique, the use of control conditions, and the definition of criteria of change, would each be associated with articles of better reporting and methodological quality. The shifts in M scores, shown in Table 3, are all in the predicted direction and are very large and reliable. It would probably be simpler to understand the M score changes as evidence of a

tendency for the methodological features to intercorrelate. When one methodological feature is present, others tend to be present, but when such a feature is absent, then none or few are likely to be present. This view is, of course, also supported by the bimodality of the M score distribution.

The results also support the prediction that reporting would be more adequate in articles indicating use of the double-blind feature, control conditions, or defined criteria for therapeutic change. All six relevant R score differences (Table 4) are in the predicted direction, and four of them are statistically significant.

SUMMARY AND CONCLUSIONS

Psychiatric journals for fiscal years 1957 and 1960 were surveyed for articles reporting research on the therapeutic value of tranquilizing and energizing drugs. Data concerning the amount of specific information reported and the use of commonly accepted methodological features were collected for each article. There were 36 per cent more articles in 1960 than in 1957. The amount of specific information commonly reported in the literature is less than has been considered desirable for adequate replicability, but there were relatively fewer very poorly reported articles in 1960 than in 1957. The predicted gain in the over-all methodological quality of the literature was not found. On the contrary, the great increase in the amount of publication in this area seems to be among articles of the least methodological adequacy. Publications originating in the VA system were of better than average reporting quality and were methodologically superior, on the whole. The use of the double-blind technique, the use of control conditions, and the definition of criteria for change were also associated with more thoroughly reported, methodologically sounder work.

*Behavioral Pharmacology in the Department of Pharmacology of the Harvard Medical School**

Behavioral pharmacology is an area of specialization within the Department of Pharmacology of the Harvard Medical School. The program of research and teaching is characterized by a joint interest in pharmacology and in the experimental study of behavior. Systematic studies applying the objective, quantitative techniques of operant conditioning to the elucidation of the behavioral effects of drugs have been going on in this department for some seven years.

The broad aim of this program is to do basic research in the field of behavioral pharmacology, research directed toward giving general, coherent, and unambiguous accounts of the psychological effects of drugs. To this end, a variety of species, including pigeons, rats, cats, monkeys, and men, have been studied in a variety of behavioral situations. Most of the experiments made use of the techniques of operant conditioning. That is, the fundamental dependent variable studied is the distribution in time of the occurrences of responses of a designated class that have specified relationships to environmental stimuli. The general method of research is to develop stable behavioral performances in animals and men under conditions that are as completely specified as possible. The dose-effect relationship for representative drugs on each of these performances is then investigated.

Currently, a primary focus of interest is the investigation of the extent to which environmental factors can modify the effects of drugs on behavior. The effects of most drugs on behavior depend upon the prevailing environmental conditions, and by changing the environment it is possible to greatly modify, sometimes even to reverse, the effect of a particular dose of a drug. In our projects, the subject's environment is changed by varying the schedule of reinforcement which maintains the performance. The effects of drugs on schedule-controlled performances have been found to change drastically under different schedules; shifts of several-fold can be obtained by changing the parameter values or the type of schedule maintaining a learned performance. Systematic studies of the relations among variables involved in simple schedules showing a high degree of drug-environment interaction are in progress.

The teaching of behavioral pharmacology to graduate students and to medical students is hindered by the student's lack of previous instruction about behavioral science. Consequently, much of the teaching of behavioral pharmacology in the course in pharmacology is concerned with systematic instruction in behavioral science. Not only are regular lectures given on behavioral pharmacology, but lecture-demonstrations and formal laboratory exercises on the effects of drugs on behavior are used to familiarize the students with the experimental study of behavior.

The Department of Pharmacology staff who are primarily concerned with behavioral pharmacology are P. B. Dews, W. H. Morse, and Marcus B. Waller. The Department has recently moved to new quarters, which provide excellent facilities for research in behavioral pharmacology. Adequate equipment and space are available, and both graduate and postdoctoral training in the techniques of both experimental psychology and pharmacology can be given.

*Prepared on request by W. H. Morse, Department of Pharmacology, Harvard Medical School, Boston, Mass.

*Conference on the Metabolism of the Phenothiazines**

A conference on the Metabolism of the Phenothiazines was held on March 10, 1961, in Atlantic City, N. J., under sponsorship of the Psychopharmacology Service Center. The conference was the second which the Center has sponsored on this subject. At the first meeting, held about 18 months ago, a group of investigators who were conducting metabolic studies of the phenothiazine drugs met at the National Institutes of Health to discuss their research. This second meeting was aimed at further assessment of the current status of the field and further identification of needs in the area of chemical methodology.

The following investigators participated:

William P. Boger, Norristown State Hospital, Norristown, Pa.
Donald Brant, Sandoz Pharmaceuticals, Hanover, N.J.
Raymond M. Burgison, University of Maryland, Baltimore, Md.
C. Jelleff Carr, Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Md.
George J. Cosmides, Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Md.
Alberto DiMascio, Massachusetts Mental Health Center, Boston, Mass.
Samuel Eiduson, Veterans Administration Center, Los Angeles, Calif.
Vivian Fishman, Hillside Hospital, Glen Oaks, N.Y.
Thomas L. Flanagan, Smith Kline & French Laboratories, Philadelphia, Pa.
Fred M. Forrest, Veterans Administration Hospital, Brockton, Mass.
Irene S. Forrest, Veterans Administration Hospital, Brockton, Mass.
Walton B. Geiger, Norristown State Hospital, Norristown, Pa.
James R. Gillette, National Heart Institute, Bethesda, Md.
Leo Hollister, Veterans Administration Hospital, Palo Alto, Calif.
Evan C. Horning, National Heart Institute, Bethesda, Md.
Chien Li Huang, Spring Grove State Hospital, Catonsville, Md.
Reese T. Jones, Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Md.
Gerald L. Klerman, Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Md.
Albert Kurland, Spring Grove State Hospital, Catonsville, Md.
Tom S. Miya, Purdue University, Lafayette, Ind.
Guy Nadeau, Hospital Saint-Michel, Archange, Quebec, Canada.
Albert Picchioni, University of Arizona, Tuscon, Ariz.
Herbert Posner, St. Elizabeths Hospital, Washington, D.C.
James B. Ragland, Baylor University College of Medicine, Houston, Tex.
David Teller, Manhattan State Hospital, New York, N.Y.
Edward J. Van Loon, Smith Kline & French Laboratories, Philadelphia, Pa.
Magdalena Wechsler, New York State Psychiatric Institute, New York, N.Y.
Robert Wiser, Wyeth Institute for Medical Research, Radnor, Pa.
Arthur Yuwiler, University of Michigan, Ann Arbor, Mich.

*Prepared by C. Jelleff Carr, Head, Pharmacology Unit, Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Md., who also organized and chaired the meeting. This report is intended as a factual, objective summary of the chief points of the discussions. Although all the comments of the conferees could not be included, the report does cover some of the research reported by certain of the participants.

The first paper was presented by Irene Forrest, who reviewed the recent publications dealing with drug metabolism and excretion of the phenothiazines, but did not discuss them in detail since authors of many of the papers were present at the meeting. In general, it was quite clear that most of the phenothiazine derivatives can be detected in urine samples. Forrest noted, however, that special difficulty is encountered with the low-dose drugs, and that two misleading reports have been made regarding the rapid, qualitative detection of several of the phenothiazines. She is preparing, for publication in the *American Journal of Psychiatry,* a review of rapid urine-testing techniques and is considering the general matter of false-positive reactions.

Forrest also described the work which has been conducted in her laboratory on the formation of free radical intermediates of chlorpromazine. These intermediates can be prepared in vitro by the action of ultraviolet light and oxygen, and presumably may be formed in vivo and identified in the urine.

Following Forrest's presentation, there was a provocative discussion of details of the manipulation of phenothiazine solutions for the formation of free radicals and the general matter of the chemical stability of the phenothiazines. Flanagan discussed the stability of phenothiazine solutions and pointed out that they are relatively stable at refrigerated temperatures in the dark. The nature of the decomposition that takes place is not known, but it is known that sunlight accelerates decomposition of phenothiazine solutions, and that ascorbic acid may be useful in retarding decomposition. It was therefore suggested that solutions be prepared daily. The pH of the solution is not critical.

It was agreed that the entire matter of decomposition, stability of solutions, and free radical formations is of chemical, pharmacological, and therapeutic significance and should be the subject of a subsequent meeting.

Horning described the gas chromatographic methods which have been developed that may be available for the determination of drugs and their metabolites. He described in general the classes of chemical compounds that are most suitable for determination by gas chromatographic techniques, and noted that the substituted phenothiazines and their derivatives can be determined quantitatively. The sensitivity of this method is .001 of a gamma or below. The high resolution of the method, which yields both quantitative and qualitative records,

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makes it valuable for separating mixtures. The technical difficulties of using aqueous biological fluids are now under study. The problems involved are not insurmountable, and it may be possible ultimately to use biological fluids directly without preliminary extraction. At present, however, suitable extraction of the sample is preferred.

A major advantage of the gas chromatographic technique is that it can be used to quantitatively separate mixtures of closely related compounds. In a single determination, a series of compounds can be identified. Horning's laboratory has not determined chlorpromazine metabolites, but the method could be used for such studies. Gas chromatographic techniques are capable of determining trace amounts of a specific compound in the presence of high concentrations (from ½ per cent to 95 per cent) of another closely related compound. Regarding thermal destruction of the compounds on the heated column, it was pointed out that while temperature control of the column is important, organic compounds employed have been found to be stable in the presence of the inert gas at the temperatures used. In other words, the sample is not decomposed by the analytical method. Free radicals, as discussed earlier, are apparently not formed in this type of analysis. Horning suggested that this technique be tried in drug metabolism studies because it may give answers to questions that cannot be answered in other ways. His laboratory is willing to assist investigators interested in exploring gas chromatographic techniques.

Yuwiler reported on the complications which drug medication causes in tests for schizophrenia which he is conducting. He feels that many positive tests are found for patients because they are on drugs, and that normal control groups give negative tests because they do not receive medication. His studies indicate that medication may introduce artifacts. He noted that urinary indican excretion is increased by chlorpromazine administration, and that use of an ion exchange resin to remove urinary indican gives a better test without false-positives. The influence of chlorpromazine—which is known to inhibit some yeasts and bacteria—on the flora of the gastrointestinal tract may change indican formation. It was also pointed out that multivitamin preparations administered to psychiatric patients may produce biochemical artifacts in studies of the metabolism of phenothiazine drugs. In addition, biochemical variations characteristic of chronic patients may pose problems. Yuwiler observed that it is difficult to measure drug effects when many positive biochemical changes are related to the types of patients.

Fred Forrest described his studies of the effects of phenothiazine drugs in vitro on tetrahymena species. He has employed a standardized culture in which viability and motility could be evaluated. The drug concentration ranged from 2 to 200 gamma per ml. The end point was the concentration that produced death by cellular shrinkage and rupture in 50 per cent of the organisms. In order of toxicity, the drugs were thioridazine > trifluprom azine > chlorpromazine > promazine. Forrest noted that the piperazine-linked drugs had a variety of toxic effects not observed with other compounds, and that these are the same drugs that are more prone to produce extrapyramidal side effects in clinical usage.

Ragland reported on the method which he has used successfully for the determination of phenothiazines. The method involves extraction of the blood, urine, feces, or tissue sample with heptane, subsequent oxidation in acetic acid, and eventual estimation by spectrofluorophotometric means. It is capable of recovering 96.58 per cent of the added drug in in vitro experiments; 3.64 per cent remains in the original solution and is not extracted by the heptane. The sensitivity of the method ranges from 0.1 to 1 μg./2 ml. of the sample. In some cases, amounts as low as 0.1 to 0.01 μg./2 ml. can be determined. Good reproducibility was obtained at concentrations of 0.1 μg./2 ml., (equivalent to 1 ml. of urine, blood, or tissue homogenate sample). Glucuronides are hydrolyzed by either alkali or β-glucuronidase. In patients receiving a single dose of thioridazine, a maximal blood level was established within 3 to 4 hours and maintained for about 14 hours. Ragland did not observe a correlation between blood level and therapeutic effect. His reported blood values agree well with those established by Eiduson for thioridazine. Most of the drug appears to be in the serum, not in the red blood cell.

In the discussion of blood values with the phenothiazines, it was pointed out that there is very likely an intestinal-hepatic circulation that accounts for the accumulation of appreciable quantities of drug in the bile. This may explain the prolonged drug effect and the relatively low blood levels. Regarding the hydrolysis of the glucuronides, Ragland stated that extraction with sodium carbonate at pH 8, or heating for 20 minutes with 2N HCl, or heating for 20 minutes with 2N Na OH, and a subsequent extraction, gave comparable figures on recovery. Hydrolysis may take place slowly by this method and, indeed, may be related to the intense agitation of the samples. The issue was raised that the analytical manipulations in this and other methods may chemically destroy labile metabolites of the phenothiazines.

It was pointed out that, in drug metabolism studies in general, the concentration of the drug and its metabolites in the tissues of the central nervous system and the spinal fluid is the important value. Blood and urine figures only reflect these concentrations.

Nadeau reported his studies of in vitro binding of drugs to globulins and albumin, pointing out that ultracentrifugation-sedimentation rates may be informative in terms of measuring the binding of drugs to blood proteins. He approached the matter on a theoretical basis and reported

that the binding action of chlorpromazine and some related drugs follows the Langmuir adsorption isotherm where $r = \frac{\text{Bound drug}}{\text{protein}}$, where r is the number of binding sites. It was possible for him to calculate the dissociation constant of the complex, and from that to calculate the number of drug molecules that will bind to protein. It may be of pharmacological significance that the various phenothiazines and imipramine are not bound to the same degree. Binding is pH sensitive and falls off sharply below pH 7.4.

Posner reported on his work on the determination of chlorpromazine metabolites in the urine of patients under prolonged medication. He has observed at least 15 different spots, and identified several, e.g., a small amount of sulfoxide, the monomethyl sulfoxide, and the didemethylated sulfoxide. At least 5 appear to be phenolic, including a basic, an acidic, and possibly a neutral compound. They were found only after the parent compound was acted upon by β-glucuronidase.

The structures of the phenolic metabolites have not been positively determined. It has been found that neither 2-hydroxypromazine nor 4-hydroxypromazine represents any of the hydroxylated metabolites of promazine.

Monomethylchlorpromazine, chlorpromazine sulfoxide, chlorpromazine-N-oxide, 2-hydroxypromazine, and 4-hydroxypromazine were compared with their parent compounds for effect on Rotorod performance and prolongation of Evipal sleeping time. Only the sulfoxide exhibited markedly reduced activity. In preliminary tests, it has been shown that 4-hydroxypromazine may possibly be more active than promazine.

Fishman summarized work of her laboratory which has indicated that the sulfoxide of chlorpromazine is not the predominant urinary metabolite in either man or dog. In fact, in man chlorpromazine sulfoxide is a minor metabolite excreted in amounts less than ½ per cent of the administered dose. She and her co-workers have identified nor_2chlorpromazine (demethylated chlorpromazine) sulfoxide as the major constituent of the nonpolar fraction (3.7 per cent), with the monomethyl sulfoxide forming 1.8 per cent, and chlorpromazine found in trace quantities of 0.2 per cent. There is a species difference with respect to the excretion of the sulfoxide as well as unaltered chlorpromazine in dog and man. In general, basic nonpolar metabolites, unconjugated phenols, and their glucuronides have been found. The corresponding sulfoxides and their demethylated derivatives have been identified. They suggest that as many as 18 to 24 metabolites may be recognized.

Teller reported on the Manhattan State Hospital study of the effect of administration of phenothiazine drugs prior to the intravenous injection of mescaline. After the drugs were administered, the blood ninhydrin-positive compounds (total amino acids) were measured. A significant fall was produced by mescaline alone, and it was postulated that active drugs capable of counteracting the mescaline effect may simultaneously block the fall of total amino acids, thus providing for assay of active compounds. In the studies conducted so far, the fall in ninhydrin-positive compounds varied: the smallest decrease occurred with chlorpromazine and the greatest with sodium amobarbital. Only with amphetamine was there a fairly close correlation between the observed clinical symptoms and variations in ninhydrin-positive compounds.

Kurland described the clinical setting at Spring Grove State Hospital, Baltimore, Md. He and Huang have conducted a one-year, very carefully controlled study of chlorpromazine metabolism in one patient. They have also studied excretion characteristics in seven patients for whom phenothiazine medication was discontinued. Estimates by paper chromatography revealed marked individual differences in excretion patterns in the amounts of the drug and its derivatives. An attempt was made to isolate the suspected hydroxy derivatives by collecting 80 paper chromatograms, dissecting the spots, and subsequently isolating the compounds. By preparing the picrates of the glucuronides from paper chromatograms, they found that as much as 65 per cent of a single dose could be excreted as the glucuronide, but there was marked individual variation. There seemed to be little correlation between the drug excretion characteristics and the return of the patient's clinical symptoms. Kurland and Huang found that from 15 per cent to a maximum of 85 per cent of a dose of a drug may be accounted for in the urine of a patient under chronic dosage. Eiduson reported only 30 per cent urinary excretion of an ingested dose of thioridazine—with 50 per cent in the feces. Forrest found, at best, only up to 50 per cent of a dose.

At the conclusion of the meeting, many of the participants expressed an interest in a subsequent meeting at which many of the unanswered questions might be considered in detail. Suggested topics for such a conference were (*a*) the matter of free radical formation in vivo and in vitro, (*b*) enzymatic mitochondrial metabolic patterns, (*c*) the chemistry of the oxidation of the phenothiazines and theoretical possibilities for active metabolites, (*d*) the relation between drug dosage form and excretion rates, and (*e*) the synthesis of phenothiazine derivatives that are suspected metabolites. The need for drug and metabolite tissue distribution studies in the brain of animals and man remains a pressing problem in this field.

*Conference on Cross Cultural Psychopharmacology**

"Cross cultural psychopharmacology" was the subject of a small, invitational conference held on May 1, 1961, in Bethesda, Md. The conference was sponsored by the Psychopharmacology Service Center and arranged by George J. Cosmides of the Center's Pharmacology Unit. In addition to staff members of the PSC and the Research Grants and Fellowships Branch of the NIMH, the participants were anthropologists, botanists and ethnobotanists, and pharmacognosists and phytochemists. William A. Caudill and Stanley Diamond of the NIMH's Laboratory of Socio-Environmental Studies not only took part in the conference but were active in planning and organizing it.

The anthropologists were: Stephen T. Boggs, American Anthropological Association; Charles O. Frake, Stanford University; Zachary Gussow, Seton Hall College of Medicine and Dentistry; William A. Lessa, University of California at Los Angeles; Richard W. Lieban, Woman's College of the University of North Carolina; and Benjamin D. Paul, Harvard University.

The botanists and ethnobotanists were: Maynard W. Quimby, Massachusetts College of Pharmacy; Robert F. Raffauf, Smith Kline & French Laboratories; David Rogers, New York Botanical Gardens; Richard Evans Schultes, Botanical Museum of Harvard University; and John W. Thieret, Chicago Natural History Museum.

The pharmacognosists and phytochemists were Norman R. Farnsworth, University of Pittsburgh; Edward Leete, University of Minnesota; Egil Ramstad, Purdue University; Arthur W. Schwarting, University of Connecticut; and Heber W. Youngken, Jr., University of Rhode Island.

Raymond M. Burgison of the University of Maryland School of Medicine and Sherman Ross of the American Psychological Association served as consultants.

Purpose and Goals. "Nature" has been a fruitful source of valuable drugs. Witness morphine, curare, digitalis, quinine, ephedrine, reserpine, the endocrine drugs, and antibiotics. The staff of the PSC and some of its consultants discerned a need to examine the possibilities of work with natural products, such as plants, and also to study use of medicinal plants, especially in primitive cultures. This area of research has been called "cross cultural psychopharmacology." The conference, then, was organized for exploratory and planning purposes. The participants were invited to present some of their experiences in related research, discuss pitfalls and problems that might be encountered, and make suggestions and recommendations concerning the desirability, feasibility, and attributes of a possible research program in this area.

Approaches to Cross Cultural Psychopharmacology. One approach was focused on mass screening of plants to identify any active components that might be valuable drugs in modern medicine. The extreme view was that all—literally hundreds of thousands—of the plants in any one area should be sent to the laboratory for testing. This would be done with no, or minimal, attention to use of the plant by the inhabitants of the region. Such screening would inevitably pick up any plants that the local medicine man or shaman happened to be prescribing. The other point of view emphasized the anthropological study of the plants and medicines used in other cultures, with observations of the way in which they are used and how they fit into the cultural setting.

How to conduct research in cross cultural psychopharmacology was discussed at length, and many forms of the "team" approach were described. Some participants favored a team made up of anthropologists and ethnobotanists going into the field together. Others preferred a looser organization, such as a consultant or advisory team, with the botanists "backstopping" and guiding the anthropologists, and vice versa.

Problems. There seems to be no dearth of problems. Among those mentioned were difficulties in collection, preservation, shipping, and identification of the plant specimens. Completely accurate botanical information is a *sine qua non.* Climatic conditions and plant diseases are important variables.

Lack of trained personnel to engage in cross cultural psychopharmacology is a major problem. Most anthropologists have not had the necessary botanical experience to collect and identify plants, and many botanists do not seem to be concerned with social and cultural factors when they go into primitive societies to work.

Suggestions and Recommendations. Continued and increased communication among scientists interested in this field was considered essential. Literature reviews, especially deep and careful analyses of existing botanical and anthropological surveys, could reveal much information and reduce duplication. A clearinghouse and a coordinating committee could be established. Finally, the NIMH might publicize in appropriate ways the availability of support, through the existing grant and fellowship programs, for research and training in cross cultural psychopharmacology.

*In order to include information about this conference in this issue of the *Bulletin*, the staff of the Scientific Information Unit prepared this brief digest. A full report on the conference will be written by George J. Cosmides.

Psychopharmacology Abstracts, *A New Abstracting Service*

The first issue of *Psychopharmacology Abstracts,* a monthly journal containing brief, noncritical abstracts, came off the press in early April. Everyone who receives the PSC *Bulletin* has also been on the mailing list for the *Abstracts* partly as a way of announcing this new service. Separate mailing lists will be established later, and investigators may choose to receive only the *Bulletin,* only the *Abstracts,* or they may receive both publications. All investigators now on the *Bulletin* mailing list will be put on the mailing list for the *Abstracts* unless they specifically ask not to receive it; they do not have to write to the Scientific Information Unit of the Psychopharmacology Service Center unless they do *not* want the *Abstracts.*

This new abstracting service is a supplement to the PSC Scientific Information Unit's activities and is an integral part of the Unit's work. As most *Bulletin* readers know, the Information Unit has a large collection of reprints, monographs, manuscripts, and books in the field of psychopharmacology. This collection is used to answer inquiries and to prepare reference lists and bibliographies, handbooks, review articles, and other informational materials. The documents are available to members of the PSC staff and visitors to the Center. Abstracts have been written for many of them, but these, also, are accessible only to PSC staff and investigators who actually come to the Center. In addition, an "acquisitions" or "accessions" list has been prepared weekly. This list was sent to PSC staff, and to several investigators who specifically requested it. Although the acquisitions list was somewhat valuable in showing recently published articles and as an inventory of documents in the collection, its value was limited, first because reference citations alone do not contain much information, and, second, because the list was seen by relatively few people. The possibility of distributing the list more widely by publishing it in the *Bulletin* was considered. But, then, it was thought, why not provide more information than just the citation? Why not have an abstract as well?

Because of limitations of PSC staff time, a contract was let to a nonprofit organization specializing in the preparation of abstract journals. This organization is also searching the literature, with guidance from the PSC staff.

As soon as an article, book, or monograph is abstracted, it is added to the PSC document collection. Unfortunately, it is not feasible at present for the Scientific Information Unit to send copies of the complete document upon request, but the author's address is given in the *Abstracts* to make it easier for investigators to obtain reprints of articles that they want to read in full. Perhaps someday the Unit will be able to offer this service.

Psychopharmacology Abstracts, at least for the present, is an abstracting, not an indexing, service. The index for each issue is a relatively broad, simple type of index that can be compiled very quickly. It is not intended to be a complete and cross-referenced depth index. The Information Unit later indexes and codes each article in detail for retrieval of information for retrospective searching to answer inquiries, and has a separate program for such indexing. A description of this indexing system and plans for expanding it will appear in a later issue of the *Bulletin.* However, a cumulative index for the *Abstracts* will be published annually.

AIMS OF THE *ABSTRACTS*

Psychopharmacology Abstracts is planned to meet the following criteria: (*a*) rapid publication, (*b*) world-wide coverage of the current literature, (*c*) careful selection for a specific audience.

Rapid Publication. Psychopharmacology Abstracts is essentially a "current awareness" service, and immediate dissemination is emphasized. Every effort is made to write and distribute the abstract within three to six weeks after appearance in the primary journal. The requirement of rapid publication does place certain limitations on production of the journal, such as the type of indexing and use of typescript and offset printing, but some sacrifices must be made for speed.

Coverage and Scope. A primary reason for launching the abstracting service is that the field of psychopharmacology straddles several traditional scientific disciplines—psychiatry, medicine, anthropology, psychology, pharmacology, neurophysiology, botany, biochemistry, organic chemistry—and the literature is found in many scattered sources. The psychologist probably does not regularly see the biochemical journals, and the organic chemist does not have ready access to psychiatric journals. Similarly, no single established abstracting and indexing

service covers all the materials that interest psychopharmacologists, which necessitates a search not only of many primary sources but also of several secondary sources.

The literature sources from which the abstracts are obtained are as extensive as possible. Every psychiatric, psychological, and pharmacological journal received by several large libraries in Philadelphia and Washington is searched. All journals in other scientific fields in which psychopharmacological reports might appear are also regularly scanned. Books and monographs are abstracted also. Later this year a list of journals regularly searched and a more definitive description of other sources of information will be published.

The content or subject matter—actually a definition—of "psychopharmacology" has been a recurring problem, which became particularly acute when it was necessary to decide what to include in the *Abstracts*. There seem to be almost as many meanings and connotations of the term as there are investigators doing research in what they call "psychopharmacology." Usage ranges from a rather narrow definition, such as "treatment of mental illness with new drugs," to a more all-encompassing definition such as "all research and clinical practice that is relevant to, or has implications for, the effects of drugs on human and animal behavior." The broader definition might easily expand into all research in psychiatry and neuropharmacology, and much of psychology, pharmacology, neurophysiology, and other fields of science. Although wide coverage is desirable, a specialized information service and abstract journal cannot become so general as to lose the advantages of specialization.

For practical purposes, then, psychopharmacology is considered to be the study of the effects of drugs on behavior, normal or abnormal, in animals or in human beings. "Drug" in this context means any chemical substance, exogenous or endogenous, that has an effect on behavior. Thus, psychopharmacology would be concerned with all clinical studies of drugs in psychiatry, including side effects, toxicology, and follow-up reports. It would cover studies of drug effects on normal behavior—e.g., learning, motivation, psychomotor performance, and any other aspects of behavior—all research on drugs affecting the behavior of animals, and studies of the sites and modes of actions of these drugs. The selection of articles on chemical synthesis has been especially difficult; in general, those studies are included whose explicit purpose is the synthesis of a new agent for psychopharmacological study. Some drugs might not be included at this stage because at the time of their synthesis the psychopharmacological potentialities are not anticipated. Studies of biochemical correlates of *behavior* (but not all neurochemistry) are included when such studies have direct implications for understanding the action of the drugs that affect behavior. Methodological studies of clear relevance to psychopharmacology are also abstracted, although this does not mean all methodological papers in psychology, psychiatry, pharmacology, and other fields are covered.

An Audience of Psychopharmacologists. Just as the coverage of journals and subject matter ranges widely but is selectively aimed at reports in psychopharmacology, *Psychopharmacology Abstracts* is tailored to a relatively small audience of investigators who are doing research in psychopharmacology. It is not written for the practitioner or for the layman—though these two groups might find materials in it of interest to them—but is specifically designed to facilitate communication among research workers. Ideally, each investigator who receives it will glance over it immediately for current, up-to-date information, and not put it on a library shelf for the elusive day when "there is more time." For this reason, with some exceptions, it is sent directly to the investigators rather than to libraries.

Psychopharmacology Abstracts is distributed gratis. Requests to be added to the mailing list should be accompanied by a brief statement of the research interest of the investigator. The main purpose in asking for this statement is to learn what research workers are doing, so that the *Abstracts* can be adapted to their interests. In a rapidly expanding field like psychopharmacology, it is especially important to know the directions in which the many research efforts are going.

Parenthetically, it might be added that gratis distribution of any publication is a risky business. Even a token subscription price is a tangible sign that the reader really wants to receive the journal. But the Psychopharmacology Service Center hopes to continue this distribution as part of its whole information service function, and trusts that those investigators (and libraries) who do not make use of the journal will ask to be removed from the mailing list.

COMMENTS, OPINIONS, AND SUGGESTIONS

As is true of most new publications, the *Abstracts* will undoubtedly change and, hopefully, improve. Although some of the more obvious imperfections will be easily corrected, the continued cooperation of all investigators who receive it is necessary if its true aims are to be achieved. All recipients of the *Abstracts* are therefore strongly urged to make suggestions and to make them as concrete and specific as possible. Comments on format, coverage, or any other aspect of the journal are invited; calling attention to inaccuracies or omissions will be particularly helpful. Send your comments to Head, Scientific Information Unit, Psychopharmacology Service Center, National Institute of Mental Health, Bethesda 14, Md.

*Psychopharmacology Service Center Program**

INTRODUCTION

During the past year several special programs have been developed which will markedly improve the clinical drug evaluation aspects of the psychopharmacology program of the National Institute of Mental Health. Interesting new research findings have continued to evolve from both the basic and clinical research projects already under way under grant support. In addition, expanded services in the areas of data analysis and scientific information are being made available to investigators in psychopharmacology.

In order to provide a better overview of the place of these developments within the broader field of psychopharmacology, they will be discussed within the context of such subareas as clinical drug evaluation, basic psychopharmacological research, and Psychopharmacology Service Center staff activities.

CURRENT CLINICAL RESEARCH

Phenothiazines and Other Tranquilizing Drugs

There are now 10 phenothiazine derivatives available for prescription use in the treatment of psychiatric conditions. All these drugs are recommended by the manufacturers for use in the treatment of schizophrenic symptomatology. Are these drugs different from one another in effectiveness? Do they differ from one another in the specific types of symptoms affected? Are any of them superior to the original drug in this group—chlorpromazine—in general efficacy or in specific effectiveness in the treatment of individual symptoms? The answers to these questions have been slow in coming, and definitive answers are still not available although recent findings show interesting trends.

First, it is clear from grant-supported studies at Spring Grove State Hospital and at the Downstate Medical Center in Brooklyn, N.Y., as well as from the Veterans Administration's multihospital studies of psychoactive drugs, that chlorpromazine is substantially more effective than promazine in the treatment of schizophrenic states. Work at Spring Grove State Hospital and work carried out by the Veterans Administration has also indicated that chlorpromazine is more effective than mepazine in the treatment of schizophrenic symptoms. The investigators at Spring Grove State Hospital report that their study fails to show mepazine to be different from inert placebo in its ability to alter psychotic symptoms. A number of investigators report that several of the other newer phenothiazines—perphenazine, prochlorperazine, thiopropazate, trifluprομazine, and trifluoperazine—have appeared on the basis of uncontrolled early clinical trials to be effective in the treatment of schizophrenic symptoms at lower doses than chlorpromazine. It has yet to be shown, however, that any of these drugs possess specific advantages over chlorpromazine in their ability to reduce psychotic symptoms when used at appropriate dosages. Results from a multidrug controlled comparative study carried out at Spring Grove State Hospital and from the Veterans Administration's most recently completed controlled cooperative drug study show a tendency for trifluprομazine to be somewhat superior to chlorpromazine in over-all clinical efficacy. A study recently completed at Spring Grove State Hospital has shown a tendency for prochlorperazine and perphenazine to be a little less effective than chlorpromazine. Perphenazine was found likely to produce undesirable neurological side effects. The group at Spring Grove State Hospital is now proceeding to compare chlorpromazine and trifluprομazine with the other newer phenothiazines: thiopropazate, trifluoperazine, thioridazine, and fluphenazine.

A large-scale comparative study of the effectiveness of chlorpromazine, prochlorperazine, perphenazine, and trifluprομazine and placebo in chronic schizophrenic patients has just been completed at Napa State Hospital and the data are being analyzed. Preliminary results as reported by the investigators indicate that these drugs, as a group, are very much more effective than placebo in producing symptomatic improvement and in enabling patients to be returned to the community. More refined analyses now under way will provide evidence concerning qualitative differences between these drugs.

One of the most interesting new phenothiazines is thioridazine. This drug produces substantially no neurological side effects common to other clinically potent phenothiazines. Preliminary studies carried out by grantees working at the Palo Alto Veterans Administration Hospital and the Nebraska Neuropsychiatric Institute support the thesis that this drug is at least as potent as chlorpromazine in the treatment of chronic schizophrenic patients and is less likely than chlorpromazine to produce neurological side effects.

*This report was prepared in February 1961 as background information for the Director of the National Institute of Mental Health, Public Health Service, U.S. Department of Health, Education, and Welfare, in connection with fiscal year 1962 appropriations hearings. It has been printed in Hearings before the Subcommittee on Appropriations, House of Representatives, Eighty-Seventh Congress, First Session. (Subcommittee on Departments of Labor and Health, Education, and Welfare and Related Agencies Appropriations, John E. Fogarty, Chairman.) Department of Health, Education, and Welfare, Part 2. Public Health Service. Washington, D.C.: Government Printing Office, 1961.

Many investigators have suggested that to be effective in the treatment of psychotic symptoms, a phenothiazine must produce unpleasant neurological side effects. The systematic study of the relationship between the production of neurological side effects and clinical potency will have both specific practical implications for the use of existing drugs and for the development of newer and more effective phenothiazines. For this reason, the Psychopharmacology Service Center, on the recommendation of the Advisory Committee on Psychopharmacology and the National Advisory Mental Health Council, has developed a nine-hospital cooperative study of the effectiveness of three phenothiazine derivatives—thioridazine, chlorpromazine, and fluphenazine—in the treatment of acute schizophrenic patients. Of all the phenothiazines now in general clinical use, thioridazine is the least likely to produce neurological side effects, and fluphenazine is probably the most likely to do so. It is important to determine whether either drug possesses clinical superiority over, or qualitative differences from, chlorpromazine. The study now under way will, in addition, provide valuable information concerning the differential responsiveness of male and female patients to the three drugs. Since the nine hospitals have been selected to represent a broad spectrum of clinical treatment milieu, ranging from private hospitals and university psychiatric pavilions to psychiatric wards in city hospitals and the admission services in State hospitals, the study will cast some light on the relative effectiveness of drug treatments in different hospital environments and will provide the first systematic data relevant to the long-standing question, "Are drugs more effective in public mental hospitals than they are in university psychiatric pavilions?" The broad range of psychiatric hospitals involved will also insure that the final results will be more representative of the true effectiveness of these drugs than would results obtained from studies in a single hospital or in a more homogeneous group of hospitals.

The need for this multihospital study involving a variety of hospital milieu has recently been underlined by a report from a grant-supported study carried out at a very well staffed and equipped psychiatric facility which failed to show either chlorpromazine or reserpine to be superior to an inert placebo in the treatment of recently hospitalized psychiatric patients for whom tranquilizing medication appeared indicated.

The results of the multihospital study will complement the results obtained from a concurrent cooperative study being carried out by the Veterans Administration, studying newer phenothiazine derivatives in male schizophrenic patients newly admitted to Veterans Administration hospitals. Since the population studied by the Veterans Administration is likely to be somewhat more chronically ill than the population in the nine-hospital study described above, it will be important to see whether the results obtained in the two studies are or are not the same. Since both cooperative studies will utilize a common clinical rating instrument, the Lorr scale, it will be possible to determine whether Veterans Administration patients differ significantly in type or severity of psychiatric symptoms from patients newly admitted to State or private mental hospitals.

Well-designed controlled studies of the effectiveness of meprobamate and other drugs used in the treatment of neurotic outpatients have to date produced conflicting results. Some studies show meprobamate to be superior to an inert placebo while others fail to show any difference between the two treatments. On the basis of some data from a study carried out at Johns Hopkins, it would appear that significant differences may exist among therapists in the response of their patients to meprobamate and to placebo. To examine this problem more directly, a special study of the effects of the therapist's behavior on the response of neurotic outpatients to meprobamate and placebo is now under way. The study was planned by the Psychopharmacology Service Center in cooperation with investigators at the University of Pennsylvania and Johns Hopkins University. The psychiatric outpatient units of both institutions are participating in this study. This study will be the first to formally test the hypothesis that physicians with a high level of therapeutic ardor induce greater improvement in drug-treated patients than do physicians whose attitude is more reserved and experimental. Further, it is hypothesized that the difference between drug- and placebo-treated patients will be greater in the patient groups treated by the therapeutically positive physicians. This special study is a portion of a larger special program which is concerned with the efforts of psychological set and social interaction upon drug response in both patients and normal subjects.

A group of grant-supported investigators at the University of Michigan have studied the effects of three substances, (*a*) meprobamate, the most widely prescribed mild tranquilizer; (*b*) a combination tablet advertised as a tranquilizer and sold without prescription; and (*c*) placebo, in a group of anxious neurotic subjects and a group of normal college students. Although the combination tablet contains many substances in small amounts, its alleged "tranquilizing" properties are probably attributable to its bromide content. The study showed that five tablets a day produced a significant rise in blood bromide level and occasional skin reactions of the type usually associated with bromide ingestion. Both the combination tablet and meprobamate produced greater sleepiness than did placebo, and with both drugs patients felt that more physical effort was required to carry out daily activities. Under meprobamate, patients appeared to the observing psychiatrists more rested, less tense, and to have improved psychological functioning. The combination tablet, on the other hand, appeared to produce impairment in such psychological functions as

concentration and retention. Observations by the subjects' friends also suggest that meprobamate produced an observable decrease in anxiety level, while the combination tablet principally reduced activity level. In summary, meprobamate was shown in this study to be superior to the combination tablet, a bromide-containing patent medicine, and to an inert placebo in decreasing anxiety level in anxious patients and in improving psychological functioning, whereas the combination tablet tended to slightly impair psychological functioning without providing comparable decreases in observed anxiety. Both drugs produced some sedative effect.

A study of the effects of perphenazine, a phenothiazine, on the verbal productions of psychosomatic patients at the University of Cincinnati has shown that the drug causes a significant decrease in both overt and covert manifestations of hostility in the total patient group. Patients with substantial amounts of anxiety also showed a decrease in this symptom, and the patient group as a whole showed a significant increase in feelings of general well-being resulting from treatment with the drug.

A series of studies of drugs used in the treatment of neurotic, hyperkinetic, and sociopathic children in the outpatient clinic at Johns Hopkins University has shown that neurotic children show such a high rate of improvement on placebo that no significant drug effect can even be expected. Sociopathic children have shown little or no improvement on any of the drugs (meprobamate, prochlorperazine, or perphenazine) studied to date. The first two drugs showed little effect on hyperkinetic children. The effects of perphenazine were equivocal. The rate of improvement was not significantly greater than that obtained under placebo, but those hyperkinetic children who improved under perphenazine became worse when the drug was discontined. The investigator who has carried out this research believes that further research may well identify drugs which will be effective in the treatment of hyperkinetic disorders of childhood. This research underlines, however the present general inffectiveness of drugs in psychiatric disorders of childhood with generally proven efficacy in adult psychiatric patients.

Antidepressive Drugs

A research project utilizing depressed patients from four New Jersey State hospitals is now comparing electroconvulsive therapy, iproniazid, and an inert placebo in a detailed controlled study. Preliminary results on the first half of the total patient sample to be studied reveal two important findings. First, most of the depressed patients in this study, which is, to date, restricted to women between ages 20 and 40, tend to show significant improvement even on placebo medication. Second, both electroconvulsive therapy (ECT) and iproniazid show some qualitative differences from placebo. ECT has shown over-all superiority in total symptom reduction while iproniazid produces a significant speeding of psychological functioning. A similar study comparing imipramine, phenelzine, isocarboxazid, and ECT is under way in three Massachusetts State hospitals. A preliminary analysis of the data from this study is now being carried out. Several other smaller clinical studies of antidepressant drugs are also in progress.

Early Clinical Drug Evaluation

Five grant-supported units are now actively engaged in the systematic early clinical evaluation of new drugs. Although these units have provided some useful preliminary information on such important newer drugs as thioridazine, imipramine, fluphenazine, and the monoamine oxidase inhibitors, the work now in progress falls far short of meeting the needs of the field of psychopharmacology for the expansion of research effort in this special area. Animal drug-screening techniques can still provide only very tentative information about a drug's therapeutic possibilities. All recent discoveries of new types of psychiatric drugs have been made by clinicians on the basis of studies carried out in patients.

Although the safety of new drugs and their ability to affect behavior or central nervous system activity may have been established in experimental animals, their special therapeutic properties have been first suggested by their effects in patients. An expansion of support for early clinical drug evaluation should, therefore, facilitate the discovery of other new and important drugs. In addition, the expanded support of such units should help meet the present urgent need that promising new drugs receive a more thorough clinical evaluation at an earlier stage of their development than has generally been possible heretofore. For these reasons a special program of grant support for early clinical drug evaluation units has been developed and formally announced. More than 20 grant proposals requesting support under this program had been received as of January 1, 1961, reflecting a high level of interest in work of this sort on the part of clinical investigators.

PRECLINICAL RESEARCH

An interesting comparison of four psychotomimetic agents—lysergic acid diethylamide (LSD), Sernyl (1-(1-phenylcyclohexyl) piperidine HCl), mescaline, and Ditran (a mixture of N-ethyl piperidine and N-ethyl-methyl-pyrollidine)—has been carried out in schizophrenic and sociopathic psychiatric patients at Ypsilanti State Hospital. Only one of these, Ditran, produced a clear reactivation of previously experienced acute psychotic symptoms in chronic schizophrenic patients and a delirium-tremen-like syndrome in alcoholics with a past history of delirium tremens. Sernyl produced either confused excitement or sedation, without hallucinations or other psychotic symptoms. LSD produced visual illusions and hallucinations, but these were milder than those

elicited by Ditran and were recognized as drug effects by the patients. Symptoms produced by Ditran were not so recognized. Mescaline, in the dosage used, was almost entirely lacking in psychotomimetic properties. The investigators also observed that the effects of Sernyl could be effectively suppressed by intravenous succinate. Ditran is presumed to produce psychotomimetic effects because of its potent anticholinergic properties. This theoretical mechanism of action was strongly supported by the finding that tetrahydroammacrin (THA), an Australian drug with marked anticholinesterase activity, effectively blocked the severe psychotomimetic effects of Ditran. This research group is now examining THA to see if it has any clinical utility in the treatment of psychiatric patients.

Deanol, a drug being marketed for use in the treatment of mild depressive reactions, has been hypothesized to exert its effect by increasing the amount of acetylcholine in the brain. Doubt has been cast on this theory by a study of the drug by investigators at Yale. They have been unable to produce a significant increase in acetylcholine levels in the brains of experimental animals with this drug.

A study of the effects of dextro-amphetamine, meprobamate, and placebo carried out on psychiatrically normal aged male veterans at the Veterans Administration Center in Martinsburg, W. Va., has shown that both drugs cause significant decreases in the clear-thinking factor of the Clyde Mood Scale. It is interesting that these aged subjects reported both drugs as producing undesirable effects while studies of younger subjects using the Clyde Mood Scale have reported generally pleasurable effects from both drugs.

A group at the Massachusetts General Hospital has studied the effects of amphetamine and secobarbital on the athletic performance, judgment, and mood of athletes. The most important finding was that athletes under secobarbital showed poorer performance while judging themselves to be performing better than usual. This disparity between the subjectively perceived and the real effects of the drug could produce dangerous consequences in individuals who drive under the influence of this and related drugs. Amphetamine, on the other hand, significantly improved athletic performance; the athletes showed a slight tendency to believe they had done less well than had actually been the case.

Grantees at the State University of Iowa have been studying central nervous system activity as influenced both by lesions and by drugs, and have been interested in drugs which produce predictable changes in both central nervous system activity and behavior. One compound, Tremorine, elicits a continuing rest-type tremor in the cat. They have identified the site of action of this compound and are using this well-understood drug effect as a method for gaining further information about the sites of action of other psychopharmacological agents which influence the drug-induced tremor produced by Tremorine. Another compound, imino-beta, beta^1-diproprionitrile, has been found to produce a peculiar circling and waltzing behavioral effect in mice which can be reversed by certain psychopharmacological agents. Both compounds produce abnormalities of brain function and behavior against which other psychopharmacological agents can be tested. One of the basic problems facing psychopharmacology has been the necessity of using the effects of drugs on the behavior of normal animals as the major approach to the identification of drugs which may be effective in treating abnormal states in man. Drugs like Tremorine and imino-beta^1-diproprio-nitrile, by creating specific abnormal behavioral states in animals, may form the basis of promising new approaches to the screening of psychiatric drugs in behaviorally abnormal animals.

Investigators at Yale have prepared an outstanding review article on the effects of drugs on motivation in animals. The article incisively points out the many confounding variables which may complicate animal behavioral studies of drug effects, and underlines the need for using multiple approaches to clearly demonstrate specific drug effects on anxiety, fear, conflict, learning, etc., psychological functions which appear on the surface to be simple and straightforward, but are in reality highly complex. For example, work at Yale has followed up work done earlier at Northwestern which had appeared to show that alcohol prevented an experimentally induced neurotic conflict from interfering with hunger-motivated behavior in cats. The group at Yale has shown that this type of experimental situation must be separated into two components—a hunger-induced drive to approach the food and a fear-induced drive to avoid the food box where, the animal has learned, he will be punished. They have clearly shown that the strength of the hunger drive was unaffected by alcohol, while the fear-motivated avoidance drive was significantly reduced by alcohol. The group at Yale feels that these results obtained in the rat may help to explain some of the paradoxical social effects of alcohol; e.g., a person whose fear or anxiety has made him repress underlying hostile tendencies will, when drunk, be more inclined to be overtly hostile, while a person with strong underlying amorous drives which are repressed because of anxiety or fear will, under alcohol, become overtly affectionate.

The studies by the Yale group on tranquilizing and sedative drugs also serve to underline the problems of studying in animals the anxiety- and fear-reducing properties of drugs. For example, chlorpromazine, a potent tranquilizer, appears to have fear-reducing properties when studied in a situation in which the rat must choose between continuing to push a lever for food and retreating to a safe "island" in the cage after being warned by a sound that a painful shock is imminent. It also increases the animal's ability to keep on pressing a bar

for a food reward in the presence of a sound which precedes a painful and escapable shock. On the other hand, chlorpromazine does not increase the hungry animal's ability to run down an alley to get a food reward when he knows he will receive a painful shock toward the far end of the alley. Alcohol, on the other hand, markedly alleviates the decrement in alley-running performance produced by fear of a painful shock, but has little or no effect on the animal's ability to keep from retreating to a safe "island" well in advance of an incipient shock and has only a modest ability to maintain food-getting activity during the warning period before an unavoidable shock occurs. Sodium Amytal, a barbiturate, is quite effective in maintaining hunger-motivated behavior and in suppressing the effects of "fear" in all three of the experimental situations described above. The relationships between the different effects of these three agents under the three "anxiety"-producing procedures described above and their effects on normal, psychoneurotic, and psychotic human subjects remain to be determined.

CONTRACTS

A contract for the synthesis of chemical compounds related to serotonin has been awarded and is now in its second year. These compounds are currently being utilized by several grant-supported investigators, as well as by several scientists in the National Institute of Mental Health and the National Heart Institute. One compound synthesized under this contract, kynuramine, has formed the basis of a new and simplified method for the determination of monoamine oxidase (MAO) inhibition. This method, developed by an investigator in the National Heart Institute, now places such determinations within the scope of the usual clinical laboratory available to clinical investigators in most well-equipped hospitals. Previous methods for measuring MAO activity in man required elaborate and complex instrumentation not generally available. Since several antidepressive drugs appear to act through their MAO-inhibiting properties, this new technique provides a simplified method for determining whether patients treated by these drugs are being given a sufficient dosage to achieve the desired pharmacological effect.

A contract has also been awarded for the synthesis of a number of phenothiazine derivatives which have been tentatively identified as naturally occurring metabolites of chlorpromazine and other phenothiazines in general clinical use. The availability of modest amounts of such compounds with proven chemical structure will greatly facilitate research on the metabolism of phenothiazine derivatives, since the small amounts of these metabolites isolatable from the urine of patients or animals make positive identification impossible when standard compounds of known structure are not available.

In the two contracts described above and in the subsequent developments of this program, the aim is to support the initial synthesis of chemical compounds which are needed by grant-supported investigators in psychopharmacology and are not available through the usual commercial channels. Once the syntheses have been completed and small amounts of the substances have been made available to interested grantees and research workers at the National Institutes of Health, it is hoped that additional amounts of these compounds will then become readily available through usual commercial channels.

INFORMATIONAL ACTIVITIES IN PSYCHOPHARMACOLOGY

The Scientific Information Unit is continuing its effort to facilitate and improve communication of research findings in the field of psychopharmacology. During the year a large number of bibliographies and reference lists were compiled and distributed. Examples are reference lists on the following drugs: pheniprazine, nialamide, phenelzine, triflupromazine, amphenidone, iproniazid, chlormethazanone, and imipramine. Bibliographies on "research methodology in clinical psychopharmacology," and "placebo problem in psychopharmacology" were compiled as one contribution to the Center's mission of improving the quality of clinical investigations of drugs. Information on the pharmacological action of drugs was provided in a detailed and annotated bibliography on the metabolism of, and analytical methods for, phenothiazine derivatives used in psychopharmacology. In addition, a large number of bibliographic searches were done, and reference lists compiled in answer to specific inquiries.

The collection of documents, including reprints, books, manuscripts and monographs has expanded considerably. There are now approximately 12,000 documents on file. Much of the activity of the Unit has been devoted to searching the scientific and medical literature, collecting the documents, cataloging and indexing them, and maintaining the document collection. The collection has been used constantly by members of the Center staff and has been of great assistance to them in providing background information necessary to the special projects on which they are working.

With the increasing number of new chemical compounds of importance to psychopharmacology, it has been imperative to have speedy access to information about them. One major project completed during the year was the establishment of a complete and cross-referenced file of all drugs relevant to psychopharmacology. For each drug, information has been obtained on its chemical formula and structure, chemical name, generic or common name, and trade names used in the United States and in other countries. Each drug is also keyed by code number to the document collection, making it possible to retrieve all pertinent reports on it. Maintaining this file will be a continuing activity of the Unit.

Because the document collection and dissemination of information encompasses materials in all languages, it has been necessary to provide extensive translation services, both for indexing purposes and for complete translation of documents. The Slavic languages generally present the greatest problems. An expert in Slavic languages was, therefore, added to the staff, and translations of Russian articles are now available.

The Psychopharmacology Service Center *Bulletin* is one of the chief means by which information has been disseminated. The *Bulletin* is now sent to approximately 3,500 investigators in the field of psychopharmacology, of whom approximately 1,500 are located outside the United States. Of special interest during the past year were the issues devoted to an annotated listing of all Institute grants in psychopharmacology and a tabular presentation of drugs used in psychiatry. The table listing the drugs was especially well received; over 5,000 copies have been distributed, many of them for teaching purposes in medical schools.

DATA ANALYSIS

During the past year the Psychopharmacology Service Center has been able to expand its facilities for the statistical analysis of data from psychopharmacological studies. This expansion will make possible the rapid and efficient processing of data coming from the nine-hospital collaborative study of phenothiazines in acute schizophrenic patients. It will also speed the analysis of data from many other studies of special interest to the Center and make possible many types of statistical analyses which have not been possible in the past.

CONFERENCES AND MEETINGS

A meeting on drugs and community care was organized by the Psychopharmacology Service Center and was attended by some 63 scientists, many of whom were grantees engaged in the study of the effectiveness of drug treatment in the maintenance of psychotic patients in the community. The proceedings included the reports of research results by a number of these investigators and detailed descriptions of a variety of methods utilized by investigators for the assessment of the psychiatric status and the social adjustment in the community of patients released from the hospital. Other aspects of research design in this area of research were also discussed. The research results reported at this meeting provided strong evidence concerning the effectiveness of tranquilizing drugs in maintaining schizophrenic patients in the community and in averting their return to the hospital when relapses occurred.

A similar meeting of grantees and other appropriate research workers and consultants interested in the evaluation of drug therapies for depression is planned for the coming year.

Recent NIMH Grants

Between January 1 and May 1, 1961, the National Institute of Mental Health awarded the following grants in support of psychopharmacological research. (The March 1961 PSC Bulletin described NIHM-supported projects in this area which were active as of January 1.) Requests for detailed information about the research should be addressed to the principal investigator of the project.

Action of Neurotropic Drugs on Mammalian Brain Cells (MY–3878). R. S. Geiger and L. G. Abood, University of Illinois College of Medicine, Chicago, Ill.

Thyroid, MAO, and Sympathomimetic Amine Interactions (MY–4435). Paul V. Buday, University of Rhode Island, Kingston, R.I.

Isolation of Toxic Substances in Schizophrenic Urine (MY–4598). Nelson S. Ging and Shigeo Fujita, Ypsilanti State Hospital, Ypsilanti, Mich.

Isolation of a Serum Factor in Schizophrenia (MY–4816). Charles E. Frohman and Jacques S. Gottlieb, Lafayette Clinic, Detroit, Mich.

Studies of Self-Stimulation of the Septal Area (MY–4855). Bertha L. Newman, University of Southern California, Los Angeles, Calif.

Effects of Prenatal Chlorpromazine on Offspring (MY–4956). Joseph Mark Ordy and Bernard H. Fox, Cleveland Psychiatric Institute, Cleveland, Ohio.

Effects of Drugs, Schizophrenia on Metabolic Patterns (MY–4957). Alvin J. Glasky and Roy R. Grinker, Michael Reese Hospital, Chicago, Ill.

Drug Sensitive Free-Operant Measures of Psychosis (MY–5054). Ogden R. Lindsley, Harvard Medical School, Boston, Mass.

Modification of Drug Response by Instructional Set (MYP–5256). Conan Kornetsky and Edward W. Pelikan, Boston University School of Medicine, Boston, Mass.

Corrigendum

The following note describing grant MY–2094 should be substituted for the one which was published on page 21 of the March 1961 PSC *Bulletin*.

MY–2094. Basic Types of Effects of Drugs on Behavior.

The relations between environmental variables and drug effects on behavior are being explored in a broad program of research in which operant conditioning techniques are being used in controlled environmental situations. The type of motivation, the nature of the response, and species differences are being investigated in pigeons, cats, monkeys, octopuses, and man. Drugs to be employed include methamphetamine, amobarbital, chlorpromazine, and epinephrine. In some of the work, morphine is being used as a reinforcer in morphine-addicted monkeys.

PETER B. DEWS AND WILLIAM H. MORSE, *Harvard Medical School, Boston, Mass.*

PSC Chemical Synthesis Program

This section contains recent developments resulting from the PSC's contract program for synthesis of chemical substances.

A STABLE SALT OF SEROTONIN

Serotonin hydrogen oxalate is now available from the Regis Chemical Company. This nonhygroscopic salt occurs as a white crystalline solid, M.P. 199–200° C, soluble in water with no contaminating external nitrogen. In some experiments, it is more satisfactory than the complex with creatinine sulfate. The Psychopharmacology Service Center supported the preparation of serotonin hydrogen oxalate as a service to investigators working in the field of indole metabolism. Communications regarding this serotonin salt should be addressed to the Regis Chemical Company, 1219 North Wells Street, Chicago 10, Ill.

C^{14}-LABELED COMPOUNDS

Contracts for the preparation of D-glucose-3-C^{14}, C^{14}-labeled carnosine, and C^{14}-labeled homocarnosine have recently been awarded by the National Institute of Mental Health as part of the Psychopharmacology Service Center's contract program for the synthesis of compounds needed for psychopharmacological research.

Preparation of the glucose, which is to be labeled at the C-3 position only, is being undertaken by Horace S. Isbell of the National Bureau of Standards, Washington, D.C. A report on his method of synthesizing D-glucose-3-C^{14} will be published so that special chemical supply companies can make the labeled glucose derivative available commercially. Since all available evidence suggests that glucose is the major source of energy for the brain, and since there is evidence that carbohydrate metabolism in the brain of mental patients may differ from that in normal subjects, it is important to determine whether psychopharmacological agents affect the metabolism of this important substrate. Glucose isotopically labeled at the C–1 and C–2 positions has been used to study brain metabolism in vivo in man. However, since the usual Embden-Meyerhoff scheme of glycolytic cleavage and alternate pathways of glucose energy metabolism involve chiefly the third carbon atom, the C–3-labeled glucose is necessary to delineate significant metabolic routes. The availability of this form of isotopically labeled glucose will permit the study of normal and abnormal metabolic patterns and, in addition, will permit investigators to study the influence of psychoactive drugs on this system in psychiatric patients.

The New England Nuclear Corporation, 575 Albany Street, Boston, Mass., will synthesize carnosine labeled with the C^{14} isotope in the β-alanine and homocarnosine labeled with the C^{14} in the γ-aminobutyric acid (GABA) chain. There may be some significance in the fact that carnosine and homocarnosine are found only in excitable tissue (muscle or nerve), homocarnosine being found only in brain. Since substances able to alter GABA levels in the brain have been shown to be of importance in neuropharmacology, it is entirely possible that a better knowledge of the metabolic functions of carnosine and homocarnosine in the brain and of the enzymes which synthesize and metabolize them will lead to the discovery of new psychopharmacological agents which would be comparable in importance to the monoamine oxidase inhibitors and capable of altering the brain level of these dipeptides. The availability of labeled carnosine and homocarnosine will make it possible to study the metabolism of these compounds. This research has been very difficult because the considerable amounts of free histamine and free γ-aminobutyric acid in the brain make it very difficult to carry out nonisotopic investigations of the metabolism of carnosine and homocarnosine.

Conferences, Meetings, and Symposia

Scores of papers relevant to psychopharmacology have been presented at meetings of scientific societies held during the past few months, and several conferences and symposia have been devoted entirely to psychopharmacological topics. Notes on a few of the meetings and lists of authors and titles of papers of most direct interest to psychopharmacology are presented in the following pages as a general service for readers who did not attend the meetings. The papers cited were selected from program materials available at the meetings. Authors' addresses are given, and information on published abstracts of the papers or plans to publish the proceedings of conferences and symposia has been included where possible.

American Chemical Society

St. Louis, Mo., March 21–30, 1961

Bound copies of *Abstracts of Papers* presented at this meeting may be purchased at $3.00 per copy to ACS division members or $4.00 to nonmembers. Orders should be sent with check to Special Issue Sales, American Chemical Society, 1155 Sixteenth Street NW., Washington 6, D.C.

Burger, Alfred, and Standridge, Robert (University of Virginia, Charlottesville, Va.), Marchine, Paolo (S. E. Massengill Co., Bristol, Tenn.), and Stjernström, Nils E. (Kungl. Tekniska Högskolan, Stockholm, Sweden) Synthesis of smallring compounds for pharmacodynamic studies.

Burger, Alfred, Zirngibl, Ludwig, and Davis, Charles S. (University of Virginia, Charlottesville, Va.), Kaiser, Carl, and Zirkle, Charles L. (Smith Kline & French Laboratories, Philadelphia, Pa.) Derivatives of 2-phenylcyclopropylamine.

Byers, Sanford O., Friedman, Meyer, St. George, Shirley, and Rosenman, Ray H. (Harold Brunn Institute, Mount Zion Hospital and Medical Center, San Francisco, Calif.) The urinary output of 3-methoxy-4-hydroxy mandelic acid in "coronary-prone" and "coronary-resistant" men.

Heitmeier, Donald E., Spinner, Ernest E., and Gray, Allan P. (Irwin, Neisler and Co., Decatur, Ill.) The preparation and properties of hydroxyphenylalkylaminopyrimidines.

Robison, Michael M., Lucas, Robert A., MacPhillamy, H. B., Dziemian, R. L., Hsu, I., Kiesel, R. J., and Morris, M. J. (CIBA Pharmaceutical Products, Summit, N.J.) The development of nonhypotensive sedation drugs from methyl reserpate.

Salvador, Richard, and Burton, Robert Main. (Washington University School of Medicine, St. Louis, Mo.) The effect of chlorpromazine on nicotinamide methylpherase.

West, Robert A., and Hitchings, George H. (Wellcome Research Laboratories, Tuckahoe, N.Y.) The preparation of 4-substituted aminopyrrolo [2, 3-d] pyrimidine derivatives.

American Orthopsychiatric Association

New York, N.Y., March 23–25, 1961

Kraft, Irvin A. (Baylor Medical School, Houston, Tex.) A study of school phobias treated primarily by psychological methods.

Workshop on Drug Therapy as Part of Treatment of the Disturbed Child, chaired by George J. Lytton, Greater Kansas City Mental Health Foundation, Kansas City, Mo., and Dane G. Prugh, Strong Memorial Hospital, University of Rochester, Rochester, N.Y. Resource participants: Paul C. Benton (Tulsa Child Guidance Clinic, Tulsa, Okla.), Hunter H. Comly (Children's Center of Metropolitan Detroit, Detroit, Mich.), Seymour Fisher (Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Md.), Irvin A. Kraft (Baylor Medical School, Houston, Tex.), Maurice W. Laufer (Emma Pendleton Bradley Hospital, Riverside, R.I.), Reginald S. Lourie (Children's Hospital, Washington, D.C.), Albert J. Solnit (Yale University School of Medicine, New Haven, Conn.), Norman L. Tolo (Child Guidance Center, St. Joseph, Mo.), and Ivan T. Vasey (University of Rochester Medical School, Rochester, N.Y.).

Workshop on Management of the Patient in the Community Who Has Been Discharged on Drug Treatment from the Mental Hospital, chaired by Donald M. Carmichael, Mental Hygiene After Care Clinic in New York City, Brooklyn, N.Y. Resource participants: David Engelhardt (State University of New York, Downstate Medical Center, Brooklyn, N.Y.), Arthur Garfinkel (New York, N.Y.), Else B. Kris (New York State Department of Mental Hygiene, New York, N.Y.), Katherine LeVan (Manhattan After Care Clinic, New York, N.Y.), and Roslyn Richmond (Mental Hygiene After Care Clinics, Brooklyn, N.Y.).

Symposium on Biochemistry of Schizophrenia, chaired by Paul H. Hoch, State of New York Department of Mental Hygiene, Albany, N.Y. The individual presentations were: "A Pathophysiological Mechanism in Schizophrenia," by Jacques S. Gottlieb and Charles E. Frohman (Lafayette Clinic, Detroit, Mich.); "Correlation between Amine Metabolism and Activity of Psychosis in Schizophrenic Patients," by Harold E. Himwich and Gunter G. Brune (Galesburg State Research Hospital, Galesburg, Ill.); and "Biological Factors in the Causation of Schizophrenia," by Ian Gregory (University of Minnesota, Minneapolis, Minn.).

Eastern Psychiatric Research Association Symposium on Depression

New York, N.Y., March 4, 1961

Although some of the papers at this symposium dealt with the treatment of depression generally, most of them were devoted to studies of amitriptyline (Elavil), an antidepressive compound developed by Merck Sharp & Dohme.

Holt opened the symposium by reviewing the importance of depression in general psychiatric practice. He and other participants emphasized the frequency with which depression is encountered in a general hospital setting and the importance of early diagnosis and prompt treatment, especially when suicidal tendencies are apparent. The remainder of the morning session was devoted to Vernier's, Alexander's, and Ostfeld's papers dealing with the basic animal or human psychopharmacology of amitriptyline. Like imipramine, amitriptyline is not an MAO inhibitor, and it was, in fact, amitriptyline's close chemical and pharmacological similarity to imipramine which first suggested the possibility of its usefulness in the treatment of depression. Pharmacologically, it possesses potent anticholinergic, antihistaminic, antiserotonin, and CNS depressant actions. Its inhibitory effects on gastric secretion in man and in animals suggest that it may also be found effective in the treatment of peptic ulcer.

EEG and behavioral findings reported at this meeting indicate that amitriptyline depresses cortical EEG activity and conditioned reflex responses in animals. In trials carried out with normal human subjects, Ostfeld found that neither chronic nor acute administration caused significant changes on the Clyde Mood Scale or the Apparent Horizon Test, the latter being a perceptual test which reflects mood and affect. In a trial Ostfeld carried out with a small sample of depressed patients, however, amitriptyline did affect performance on those measures: the patients showed improvement on the "depression" and "friendly" scores of the Clyde Mood Scale, on performance on the Apparent Horizon Test, and on clinical ratings as well.

The afternoon session was devoted largely to reports of clinical trials of amitriptyline. They consistently showed that approximately 50 to 75 per cent of severely depressed patients could be expected to improve significantly within two or three weeks on dosages ranging from 150 to 200 mg. daily. Symptoms singled out as most likely to respond to the drug included depressed mood, anergia, anxiety, tension, social withdrawal, loss of appetite, poor sleep, and apathy. Although patients presenting schizophrenic-like symptoms, especially active delusions or hallucinations, usually were not helped by the drug, there were differences of opinion about whether the drug was useful in the treatment of underactive and withdrawn schizophrenics. The majority felt that amitriptyline tended to aggravate the psychotic symptoms of schizophrenic patients and should therefore not be used with them, but Feldman and others argued that the drug-induced changes in symptoms provided an opportunity for examining alternate approaches to the treatment of chronic, withdrawn schizophrenics.

Amitriptyline's side effects were reported to be similar to those observed with imipramine, though they have tended to occur less frequently and have seldom been distressing. Among them were blurred vision, dizziness, dry mouth, nausea, nasal stuffiness, skin rash, and sweating. It was noted, however, that a small percentage of patients may develop mild hypomanic excitement, and that more severe side effects, e.g., collapse and toxic delirium, may possibly occur on doses in excess of 200 mg. daily, especially if the drug is administered parenterally rather than orally. So far, there has been no evidence of liver or blood complications.

Long-term use of the drug with depressed patients, especially those who are subject to recurrences or relapse, was strongly recommended. Both amitriptyline and imipramine, because of their low toxicity, were considered by some, Ayd, in particular, to be better suited for maintenance therapy than the MAO inhibitors.

The danger of administering two or more antidepressive drugs simultaneously was stressed by many participants. Serious toxic reactions—e.g., severe dizziness, collapse, restlessness, profuse sweating, hyperpyrexia, and even death—were reported to have occurred in a number of cases when an MAO inhibitor was combined with either imipramine or amitriptyline.

The symposium participants and titles of their papers are listed below:

Alexander, Leo. (Tufts University School of Medicine, Boston, Mass.) Objective evaluation of anti-depressant therapy by conditional reflex techniques.

Ayd, Frank, Jr. (Franklin Square Hospital, Baltimore, Md.) Comparative clinical experience with antidepressants. Discussed by O. H. Arnold (University of Vienna, Vienna, Austria).

Dorfman, Wilfred. (State University of New York, Downstate Medical Center, Brooklyn, N.Y.) Recent clinical studies of chemotherapy of depression. Discussed by Herbert Freed (Temple University School of Medicine, Philadelphia, Pa.).

Dunlop, Edwin N. (Fuller Memorial Sanitarium, South Attleboro, Mass.) Management of depression in private practice.

Feldman, Paul. (Topeka State Hospital, Topeka, Kans.) Relative merits of psychotherapy and chemotherapy. Discussed by Louis Linn (Mt. Sinai Hospital, New York, N.Y.).

Holt, William L. (Albany Medical College, Albany, N.Y.) Depression; psychopathology, incidence, impact, recognition, theories.

Ostfeld, Adrian. (University of Illinois College of Medicine, Chicago, Ill.) Measurement of depression by perceptual testing. Discussed by David Wechsler (New York University College of Medicine, New York, N.Y.).

Saunders, John C., and Kline, Nathan. (Rockland State Hospital, Orangeburg, N.Y.) Review of antidepressant therapy among chronc hospitalized patients. Discussed by Henry Brill (State of New York Department of Mental Hygiene, Albany, N.Y).

Vernier, Vernon. (Merck Sharp & Dohme Research Laboratories, Philadelphia, Pa.) Psychopharmacology of antidepressants. Discussed by Gerald L. Klerman (Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Md.).

Wilcox, Paul H. (Traverse City, Mich.) EST vs. drugs. Discussed by David J. Impastato (New York University College of Medicine, New York, N.Y.).

Veterans Administration Sixth Annual Research Conference

Cincinnati, Ohio, March 27–29, 1961

About 250 research investigators attended the Sixth Annual Research Conference of the Veterans Administration Cooperative Chemotherapy Studies in Psychiatry and Broad Research Approaches to Mental Illness. As in previous years, the participants included not only key research personnel from the VA, but also a number of guests from the academic world, State and Federal agencies and institutions, and other organizations outside the VA.

There were preliminary reports on the VA's Cooperative Study No. 5, chemotherapy of depression, No. 6, an evaluation of several drugs in the treatment of newly admitted schizophrenic patients, and the cooperative study with psychiatric outpatients. In addition, the PSC-NIMH nine-hospital collaborative study of phenothiazines in the treatment of newly admitted schizophrenics was described.

The four symposia on the conference program dealt with (*a*) neurophysiological and endocrinological studies in relation to experience, (*b*) approaches to the classification of psychiatric patients, (*c*) prediction of individual patient response to therapy, and (*d*) multivariate approaches to research in mental illness. Other features of the program were study groups organized for the purpose of discussing research proposals relating to chemotherapy and other areas, and the presentation of some 30 individual research papers. One of the papers, "The Reporting and Design of Research on Psychiatric Drug Treatment," appears elsewhere in this issue of the PSC *Bulletin*.

The transactions of the conference are being edited and are expected to be available later this year. Further information about the conference and the publication of the transactions may be obtained from Mr. Clyde J. Lindley, Executive Secretary, VA Cooperative Chemotherapy Studies in Psychiatry, Psychiatry and Neurology Service, Veterans Administration, Washington 25, D.C.

Conference on Some Biological Aspects of Schizophrenic Behavior

New York, N.Y., April 6–8, 1961

This conference was sponsored by the New York Academy of Sciences. The proceedings will be published in the *Annals of the New York Academy of Sciences.*

Albaum, Harry G. (Brooklyn College, Brooklyn, N.Y.) The effect of CNS drugs on the incorporation of radioactive carbon into brain adenosine triphosphate.

Biel, John H., Nuhfer, Patrick A., Hoya, Wallace K., and Leiser, Helen A. (Lakeside Laboratories, Milwaukee, Wis.) and Abood, Leo G. (University of Illinois School of Medicine, Chicago, Ill.) Cholinergic blockade as an approach to the development of new psychotropic agents.

Brill, Henry. (Department of Mental Hygiene, State of New York, Albany, N.Y.) Reappraisal of attitudes with regard to schizophrenia.

Carr, C. Jelleff. (Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Md.) Metabolic studies on psychoactive drugs.

Cook, Leonard. (Smith Kline & French Laboratories, Philadelphia, Pa.) Drug effects on the behavior of animals.

Costa, E., Cuenca, E., Gessa, G. L., and Kuntzman, R. (National Heart Institute, Bethesda, Md.) On current status of serotonin as brain neurohormone and in action of reserpine-like drugs.

Daly, R., and Axelrod, J. (National Institutes of Health, Bethesda, Md.) Methylation and demethylation in relation to the in vitro metabolism of mescaline.

Denber, Herman C. B., Teller, David M., Rajotte, Paul, and Kauffman, Dorothy. (Manhattan State Hospital, New York, N.Y.) Studies on mescaline. XIII—The effect of prior administration of various psychotropic drugs on different biochemical parameters.

Fischer, Roland. (Columbus Psychiatric Institute and Hospital, Columbus, Ohio) Biochemical aspects of time in relation to (model) psychoses.

Freedman, Daniel X., and Giarman, Nicholas J. (Yale University School of Medicine, New Haven, Conn.) LSD–25 and the status and level of brain serotonin.

Friedhoff, Arnold J., and Goldstein, M. (New York University College of Medicine, New York, N.Y.) New developments in metabolism of mescaline and related amines.

Friend, Dale. (Peter Bent Brigham Hospital, Boston, Mass.) Metabolism of dihydroxyphenylalanine in the presence of psychoactive drugs.

Frohman, Charles E. (Lafayette Clinic, Detroit, Mich.) Steps toward the discovery and isolation of a serum factor in schizophrenia.

Fuller, John L. (Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine) Effects of drugs on psychological development.

Funderburk, William H., Finger, Kenneth F., and Drakontides, Anna. (Chas. Pfizer & Co., Groton, Conn.) EEG and biochemical findings with monoamine oxidase inhibitors.

Greengard, P., and Quinn, Gertrude P. (Geigy Research Laboratories, Ardsley, N.Y.) Metabolic effects of psychoactive drugs.

Grenell, R. G. (Psychiatric Institute, University of Maryland Hospital, Baltimore, Md.) Molecular biology in schizophrenia.

Goldman, Douglas. (Longview State Hospital, Cincinnati, Ohio) Electroencephalographic changes brought to light under Pentothal activation in psychotic (schizophrenic) patients with particular reference to changes produced by pharmacologic agents.

Gunne, L. E. (Karolinska Institute, Stockholm, Sweden) Catecholamines and narcotic drugs.

Haydu, George G. (Creedmoor Institute for Psychobiologic Studies, New York, N.Y.) Schizophrenic behavior and aspects of psychopharmacology.

Heath, Robert G. (Tulane University School of Medicine, New Orleans, La.) Brain recordings with schizophrenic behavior: some metabolic factors responsible for physiological alterations.

Hollister, Leo E. (Veterans Administration Hospital, Palo Alto, Calif.) Drug-induced psychoses and schizophrenic reactions: a critical comparison.

Ingram, Charles G. (Ypsilanti State Hospital, Ypsilanti, Mich.) Some findings in the autonomic nervous system in schizophrenia.

Kletzkin, Milton. (Wallace Laboratories, Cranbury, N.J.) Possible modes of action of psychotherapeutic agents in the treatment of mental disturbances.

Luby, Elliot D. (Lafayette Clinic, Detroit, Mich.) Biochemical, autonomic, and psychological responses to sleep deprivation: implications for the theory of schizophrenia.

Marrazzi, Amedeo S. (Veterans Administration Research Laboratories in Neuropsychiatry, Pittsburgh, Pa.) Synaptic and behavioral correlates of psychotherapeutic and related drug actions.

Pennell, Robert B. (Protein Foundation, Jamaica Plains, Mass.) and Bergen, John R. (Worcester Foundation for Experimental Biology, Shrewsbury, Mass.) A human plasma factor inducing behavioral and electrophysiological changes in animals.

Persky, Harold. (Indiana University Medical Center, Indianapolis, Ind.) Adrenal cortical and corticotropic hormone changes under experimentally induced anxiety states.

Pinson, Rex, Jr., Bloom, Barry M., and Buck, C. J. (Chas. Pfizer & Co., Groton, Conn.) Some central nervous system drugs designed from metabolic considerations.

Robins, Eli. (Washington University School of Medicine, St. Louis, Mo.) Studies on gamma-aminobutyric and N-acetyl neuraminic acid in schizophrenia.

Roizin, Leon. (Psychiatric Institute, New York, N.Y.) A review of histologic and histochemical aspects (biopsy and postmortem findings) in schizophrenic patients.

Sanders, Benjamin E., Smith, E. V. C., Flataker, L., and Winter, C. A. (Merck Institute for Therapeutic Research, West Point, Pa.) Fractionation studies of human serum factors affecting motor activity in trained rats.

Sankar, D. V. Siva, Gold, Eleanor, Phipps, Edward, and Sankar, D. Barbara. (Creedmoor State Hospital, Jamaica, N.Y.) Metabolic studies on schizophrenic children.

Sankar, D. V. Siva, Phipps, Edward, Gold, Eleanor, and Sankar, D. Barbara. (Creedmoor State Hospital, Jamaica, N.Y.) Effect of LSD, BOL, and chlorpromazine on "neurohormone" metabolism.

Schallek, William. (Hoffmann-La Roche, Nutley, N.J.) Effects of chlordiazepoxide (Librium) and other psychotropic agents on the limbic system of the brain.

Sherwood, Stephen L. (Illinois State Psychiatric Institute, Chicago, Ill.) Electrographic depth recordings from the brains of psychotics.

Sprince, Herbert. (Veterans Administration Hospital, Coatesville, Pa.) Biochemical aspects of indole metabolism in normal and schizophrenic subjects.

Sulser, F. (National Institutes of Health, Bethesda, Md.) On mechanism of antidepressant actions of imipramine-like drugs that act only in depressed states.

Szara, Stephen. (St. Elizabeths Hospital, Washington, D.C.) 6-Hydroxylation of tryptamine derivatives: a way of producing psychoactive metabolites.

Wada, John A. (University of British Columbia, Vancouver, B.C., Canada.) Behavioral and EEG effects of introventricular injection of bulbocapnine and other substances in freely moving animals.

Weil-Malherbe, H., Posner, Herbert S., and Waldrop, F. N. (St. Elizabeths Hospital, Washington, D.C.) The alleged effect of schizophrenic serum on rabbit brain catecholamines.

West, Louis J. (University of Oklahoma Medical Center, Oklahoma City, Okla.) The psychosis of sleep deprivation.

Wiseman-Distler, Mirriam, and Sourkes, Theodore L. (Allan Memorial Institute, Montreal, Canada.) Effect of 4-hydroxyindoles on the metabolism of 5-hydroxytryptamine.

Woolley, D. W. (Rockefeller Institute, New York, N.Y.) Exploration of central nervous system serotonin in humans.

Federation of American Societies for Experimental Biology

Atlantic City, N.J., April 10–14, 1961

The March 1961 issue of *Federation Proceedings* (Vol. 20, No. 1, Part 1) contains abstracts of papers scheduled for presentation. Copies of that issue may be obtained for $5.00 each from *Federation Proceedings*, 9650 Wisconsin Avenue, Washington 14, D.C.

The following list of papers was selected from the published abstracts.

Adler, Martin W. (Albert Einstein College of Medicine, New York, N.Y.) Alterations in responsiveness to reserpine following chronic brain lesions in rats.

Barbato, Libero, and Abood, Leo G. (University of Illinois, Chicago, Ill.) The inhibition of mitochondrial monoamine oxidase (MAO) by phenantroline (PTL) and phenylcyclopropylamine (PCP).

Barrett, W. E., Rutledge, R., and Plummer, A. J. (CIBA Pharmaceutical Products, Summit, N.J.) Pharmacology of SU–9064, an ether of methyl epireserpate.

Bennett, E. L., Drori, J. B., Krech, D., Rosenzweig, M. R., Diamond, M., and Abraham, S. (University of California, Berkeley, Calif., and Kaiser Foundation Hospital, Oakland, Calif.) Determination of hexokinase activity in brain.

Bergen, J. R., Koella, W. P., Czicman, J., and Hoagland, H. (Worcester Foundation for Experimental Biology, Shrewsbury, Mass.) Evoked optic potential changes induced by plasma globulins from schizophrenics.

Bindler, Elliot H., and Gyermek, Laszlo. (Geigy Research Laboratories, Ardsley, N.Y.) Influence of 5–HT antagonists on the ganglionic stimulant action of 5–HT and DMPP.

Boren, John J. (Merck Institute for Therapeutic Research, West Point, Pa.) The action of emylcamate and meprobamate on avoidance and fixed interval behavior.

Bourgault, Priscilla, and Karczmar, Alexander G. (Loyola University, Chicago, Ill.) Behavioral and pharmacological differences among certain strains of mice.

Brinling, J. C., Shopiro, T. D., and Sigg, E. B. (Geigy Research Laboratories, Ardsley, N.Y.) Unique central effects of a new non-barbiturate anesthetic.

Brown, Barbara B. (Riker Laboratories, Northridge, Calif.) CNS stimulants and electrical brain activity in spontaneously behaving cats.

Brune, G. W. (State Research Hospital, Galesburg, Ill.) Correlations between psychotropic drug effects, water and mineral metabolism in schizophrenic patients.

Burack, W. R., Draskoczy, P. R., and Weiner, N. (Harvard Medical School, Boston, Mass.) The nature of reserpine action upon adrenal gland.

Burdock, E. I., Glusman, Murray, and Zener, Julian. (New York State Department of Mental Hygiene, New York, N.Y., and Columbia University, New York, N.Y.) An animal behavior rating scale for quantification of savage behavior in cats.

Chusid, Joseph G., and Kopeloff, Lenore M. (St. Vincent's Hospital, New York, N.Y., and New York State Psychiatric Institute, New York, N.Y.) Anticonvulsant effect of Librium in epileptic monkeys.

Cooper, Kenneth, Wnuck, A. L., and Norton, Stata. (Wellcome Research Laboratories, Tuckahoe, N.Y.) Potent blocking effect of a pyrrolopyrimidine (B.W. 58–271) on the spinal polysynaptic reflexes.

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Edwards, R. E. (Sterling-Winthrop Research Institute, Rensselaer, N.Y.) Methods of detecting behavioral effects of morphine in rats.

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Feldstein, Aaron, Wong, Keith K., and Freeman, Harry. (Worcester Foundation for Experimental Biology, Shrewsbury, Mass., and Medfield State Hospital, Medfield, Mass.) The metabolism of 5-hydroxytryptophan.

Finkelstein, M., Delaney, K., Scott, C. W., and Miknius, S. (Chas. Pfizer & Co., Groton, Conn.) Pharmacologic characterization of the cardiovascular responses to xanthiol.

Fraser, H. F., Martin, W. R., Wolbach, A. B., and Isbell, H. (National Institute of Mental Health Addiction Research Center, Lexington, Ky.) Addiction liability of 1-(p-chlorphenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline HCl (I).

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Greenberg, Samuel M., Ellison, Theodore, and Mathues, Joyce K. (Smith Kline & French Laboratories, Philadelphia, Pa.) Growth "stimulation" by phenothiazines in rats fed nutritionally optimal diets.

Greenblatt, E. N., and Osterberg, A. C. (American Cyanamid Co., Pearl River, N.Y.) Effect of drugs on maintenance of exploratory behavior in mice.

Gylys, J. A., Hart, J. J. D., and Warren, M. R. (Warner-Lambert Research Institute, Morris Plains, N.J.) Chlorphentermine hydrochloride, *p*-chloro-α,α-dimethylphenethylamine hydrochloride, a new anorexigenic agent.

Hanson, Harley M. (Merck Institute for Therapeutic Research, West Point, Pa.) The effects of amitriptyline, imipramine, chlorpromazine and nialamide on avoidance behavior.

Harris, L. C. (Sterling-Winthrop Research Institute, Rensselaer, N.Y.) The effect of various anti-cholinergics on the spontaneous activity of mice.

Heise, George A., and Boff, Edward. (Hoffmann-La Roche, Nutley, N.J.) Taming action of chlordiazepoxide.

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Kissel, J. W., and Albert, J. R. (Mead Johnson & Company, Evansville, Ind.) Analgetic activity of 1,2-dimethyl-3-phenyl-3-pyrrolidyl propionate hydrochloride (prodilidine HCl).

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Koechlin, B. A., and Schwartz, M. A. (Hoffmann-La Roche, Nutley, N.J.) The metabolic fate of chlordiazepoxide.

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Lynes, T. E., and Everett, G. M. (Abbott Laboratories, North Chicago, Ill.) Pharmacological studies of a new centrally acting skeletal muscle relaxant, N-cyclopropyl-3, 5-dichloro-4-amino benzamide (MR1230).

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Petrucelli, Lawrence, M., Bulle, Peter H., and Oskoui, Mahmoud. (Georgetown University Medical and Dental Schools, Washington, D.C.) Effects of 5–HT, iproniazid and reserpine on submaxillary salivation.

Plaa, Gabriel L., Blacker, Gerry J., and McGough, Edwin C. (Tulane University School of Medicine, New Orleans, La.) Effect of CCl_4 on certain aspects of thioridazine metabolism.

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Ragland, James B., and Kinross-Wright, John. (Baylor University College of Medicine, Houston, Tex., and Houston State Psychiatric Institute, Houston, Tex.) Spectroflourimetric determination of phenothiazine tranquilizers in biological samples.

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Rodriguez, José M., Hart, E. Ross, and Marrazzi, Amedeo S. (Veterans Administration Research Laboratories in Neuropsychiatry, Pittsburgh, Pa.) The lack of carotid sinus or carotid body effect in cerebral synaptic inhibition by serotonin.

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Rowe, Robert P., Lofgren, Sally L., and Kelley, Anne. (Chas. Pfizer & Co., Groton, Conn.) Reversal of reserpine sedation with some MAO inhibitors and analeptics.

Russell, Findley E., and Bohr, Vernon C. (College of Medical Evangelists, Los Angeles, Calif.) Intraventricular injection of venoms.

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Sankar, D. V. Siva, Gold, E., Sankar, B., and McRorie, N. (Creedmoor State Hospital, Jamaica, N.Y.) Effect of psychopharmacological agents on DPN-dependent enzymes.

Sarkar, S., and Zeller, E. A. (Northwestern University Medical School, Chicago, Ill.) Characterization of two homologous monoamine oxidases.

Schapiro, H., and Woodward, E. R. (University of Florida College of Medicine, Gainesville, Fla.) The mechanism of action of reserpine on gastric secretion.

Schiffrin, M. J., Sadove, Max S., and Bruce, David L. (University of Illinois, Chicago, Ill.) Clinical study of a new analgesic, RO 4–1778/1.

Schwartz, Morton A. (Hoffmann-La Roche, Nutley, N.J.) Interrelationships between isocarboxazid (Marplan), benzylhydrazine and monoamine oxidase.

Serrone, David M., and Fujimoto, James M. (Tulane University School of Medicine, New Orleans, La.) Components involved in the potentiating action of beta-phenylisopropylhydrazine (PIH) on hexobarbital action.

Sherrod, Theodore R. (University of Illinois College of Medicine, Chicago, Ill.) The action of hydroxyzine (Atarax) on the pressor responses to epinephrine and norepinephrine.

Smith, C. M., and Walaszek, E. J. (University of Kansas Medical School, Kansas City, Kans.) Potentiation of smooth muscle stimulants by lysergic acid diethylamide (LSD).

Smith, R. L., Maickel, R. P., and Brodie, B. B. (National Institutes of Health, Bethesda, Md.) Stimulation of pituitary-adrenal axis of rat by chlorpromazine and congeners.

Soffer, Lawrence, and Gyermek, Laszlo. (Geigy Research Laboratories, Ardsley, N.Y.) The interaction of imipramine, its derivatives, and phenothiazines with 5-HT, epinephrine and norepinephrine.

Sohler, Arthur, Noval, Joseph J., Stackhouse, Stirling, and Bryan, Albert. (Bureau of Research in Neurology and Psychiatry, State of New Jersey, Princeton, N.J.) Urinary metabolites found in the rat upon administration of adrenochrome.

Soyka, Lester F., and Unna, K. R. (University of Illinois College of Medicine, Chicago, Ill.) Peripheral and central effects of N-allylnoratropine.

Stein, Larry, and Seifter, Joseph. (Wyeth Laboratories, Philadelphia, Pa.) Imipramine, chlorpromazine, and amphetamine interactions: possible mode of anti-depressive action of imipramine.

Susler, F., Watts, J. S., and Brodie, B. B. (National Institutes of Health, Bethesda, Md.) Blocking of reserpine action by imipramine, a drug devoid of stimulatory effects in normal animals.

Szara, Stephen, and Putney, Frances. (Clinical Neuropharmacology Research Center, National Institute of Mental Health, Washington, D.C.) 6-Hydroxylation of tryptamine and derivatives: the enzymatic process.

Taylor, Robert E., Jr. (University of Florida Medical School, Gainesville, Fla.) Effect of reserpine on body temperature regulation of the albino rat during exposure to cold.

Truitt, Edward B., Jr., and Ebersberger, Ethel M. (University of Maryland School of Medicine, Baltimore, Md.) Lowered convulsive thresholds to hexafluorodiethyl ether produced by drugs with differential effects on brain serotonin and norepinephrine levels.

Usdin, Vera, and Usdin, Earl. (New Mexico Highlands University, Las Vegas, N. Mex.) Effects of psychotropic compounds on enzyme systems.

Veldkamp, W., Tazelaar, A. P., Jr., and Keasling, H. H. (Upjohn Company, Kalamazoo, Mich.) Some aspects of the pharmacology of benzphetamine hydrochloride. (Phenethylamine, N-benzyl-N, α-dimethyl (+) hydrochloride; Didrex).

Verhave, Thom. (Lilly Research Laboratories, Indianapolis, Ind.) A depressant effect of methamphetamine on avoidance behavior.

Vernier, V. G., Boren, J. J., Knapp, P. G., and Malis, J. L. (Merck Institute for Therapeutic Research, West Point, Pa.) Effect of depressant drugs on thresholds for aversive brain stimulation.

Walaszek, E. J., and Chapman, J. E. (University of Kansas Medical School, Kansas City, Kans.) Bulbocapnine: an adrenergic and serotonin blocking agent.

Weil-Malherbe, H., Posner, Herbert S., and Bowles, Grace R. (National Institute of Mental Health, St. Elizabeths Hospital, Washington, D.C.) Effects of pyrogallol on brain catecholamines.

Weiss, Bernard, and Laties, Victor G. (Johns Hopkins School of Medicine, Baltimore, Md.) Effects of amphetamine, chlorpromazine, and pentobarbital on thermoregulatory behavior.

Westerbeke, Edward J., and White, Richard P. (University of Tennessee Medical Units, Memphis, Tenn.) Antagonism of phenothiazine derivatives to the EEG effects of physostigmine and amphetamine.

Wiegand, R. G., and Perry, J. E. (Abbott Laboratories, North Chicago, Ill.) DOPA, dopamine, norepinephrine, epinephrine, and serotonin mouse brain levels after N-methyl-N-benzyl-2-propynylamine.HCl and l-DOPA.

Winder, C. V., Wax, J., Serrano, B., Scotti, L., Stackhouse, S. P., and Wheelock, R. H. (Parke Davis & Co., Ann Arbor, Mich.) 1,2-dimethyl-3-phenyl-3-propionoxypyrrolidine (CI–427), an analgetic agent.

Witkin, L. B., Huebner, C. F., Galdi, F., O'Keefe, E., Spitaletta, P., and Plummer, A. J. (CIBA Pharmaceutical Products, Summit, N.J.) Pharmacology of 2-amino-indane (SU–8629), a potent, non-narcotic analgesic.

Wykes, A. A., Taylor, J. D., and Lewis, G. J. (Abbott Laboratories, North Chicago, Ill.) Rat liver 0-methyl transferase as a drug screening tool.

Yuwiler, A., and Gerard, R. W. (University of Michigan, Ann Arbor, Mich.) Urinary chromogens and the Reigelhaupt test for schizophrenia.

Zsigmond, E. K., Foldes, F. F., and Foldes, V. M. (Mercy Hospital, Pittsburgh, Pa., and University of Pittsburgh School of Medicine, Pittsburgh, Pa.) The inhibitory effect of psilocybin and related compounds on human cholinesterases.

TABLE 1.—*New Compounds Reported at Federation of American Societies for Experimental Biology*

Name of Compound	Identification	Senior Author
B.W. 58–271	2-methyl-4-benzylamino-pyrrolo [2,3-d]-pyrimidine	Cooper; Norton
benzphetamine *See* Didrex		
chlorphentermine	*p*-chloro-α,α-dimethyl-phenethylamine HCl	Emele; Glylys
CI–427, *See also* prodilidine	1,2-dimethyl-3-phenyl-3-propionoxy-pyrrolidine	Winder
Didrex benzphetamine	(+) N-benzyl-N,α-dimethyl-phenethylamine HCl	Veldcamp
G–29505	diethylamide of 2-methoxy-4-allyl-phenoxyacetic acid	Brinling
IKl, *See also* Ro 4–1778/1	1-(p-chlorophenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline	Fraser
MR 1230	N-cyclopropyl-3,5-dichloro-4-amino-benzamide	Lynes
P–2027	d-1-isonicotinoyl-2-[2-(β-phenylisopropyl-carbamyl)-ethyl] hydrazine	Rowe
prodilidine, *See also* CI 427	1,2-dimethyl-3-phenyl-3-pyrrolidyl propionate HCl	Kissel
Ro 4–1778/1 *See also* IK1	1-(p-chlorophenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline	Schriffrin
Su–7064	methyl-0-(2-tetrahydro-pyranyl) reserpate	Furness
Su–8629	2-amino-indane	Witkins
Su–8842	methyl reserpate methyl ether	Cuenca
Su–9064	methyl 18-epireserpate methyl ether	Barrett; Cuenca
	2-(β-hydroxyphenethyl-amino) pyrimidine	O'Dell

Several papers reported investigations of new or recently developed compounds which may be of psychopharmacological interest. The compounds are listed in Table 1, along with the name of the senior author of the paper in which the work was reported.

In addition to papers cited in the preceding list, a number of symposia of slightly longer papers and discussion periods were scheduled by the various societies and intersociety groups. Abstracts of papers presented in symposia are not available, but the papers are to be published in full in a forthcoming issue of *Federation Proceedings*.

Directly relevant to psychopharmacology was the intersociety Symposium on the Effects of Hallucinogenic Drugs in Man, chaired by Harold E. Himwich of Galesburg State Research Hospital, Galesburg, Ill. In the first paper, "Effects of LSD–25 and JB–318 on Tests of Visual and Perceptual Functions in Man," Adrian M. Ostfeld (University of Illinois, Chicago, Ill.) reported a study of the hallucinogenic effects of LSD in a group of congenitally blind subjects as compared with a group of blind subjects who had previously had sight for at least several years. The two groups were found to differ in the frequency with which they experienced visual and other hallucinations. The congenitally blind subjects reported olfactory, auditory, tactile, or gustatory hallucinations but no "visual" changes. The once-sighted subjects, on the other hand, did report visual hallucinations, but they also reported a greater number of other types of hallucinations than normals (i.e., sighted subjects) usually experience.

Another investigation reported by Ostfeld compared the effects of LSD and JB–318 in normal volunteers. Those who received LSD appeared to be more aware of the environment, while those given JB–318 seemed to be more concerned with body image or body changes. The two drugs also seemed to have different effects on estimation of apparent horizon and on performance on the Clyde Mood Scale. LSD increased the estimate of apparent horizon whereas JB–318 decreased it. LSD also increased the "friendly," "energetic," and "jittery" scores on the Clyde Mood Scale; JB–318 increased the "jittery" score, but decreased the "energetic" score. Both compounds increased the performance time for all three tests in the Stroop Color-Word Test.

Again demonstrating the inaccuracy in classifying all biotransformations of drugs as detoxification mechanisms, Stephen I. Szara (St. Elizabeths Hospital, Washington, D.C.) described the formation in animals of 6-hydroxy metabolites of tryptamine and tryptamine derivatives. Since 6-hydroxy amines have been shown to be psychologically active, it was suggested that their action may be important in the total effect of tryptamine and its derivatives. Confirming this, Szara's paper, entitled "Hallucinogenic Effects and Metabolism of Tryptamine in Man," reported animal studies in which behavioral threshold doses were related to rate of formation of the 6-hydroxy derivatives, a finding which was paralleled by studies of human subjects in which scores on psychological tests were related to percentage of the amines excreted as the more active 6-hydroxy derivatives.

The two remaining papers in the symposium—"Correlations between Behavior and the Urinary Excretion of Indoleamines and Catecholamines in Schizophrenic Patients as Affected by Drugs," by Guenter Brune and Gordon Pscheidt (Galesburg State Hospital, Galesburg, Ill.), and "Possible Relations of Central Amines to Behavior in Schizophrenic Patients," by Seymour S. Kety (Johns Hopkins University, Baltimore, Md.)—attempted to elucidate the relationship between psychosis and the biochemistry of the brain. Brune and Pscheidt reported an increase in tryptamine excretion which preceded increased psychotic symptomology, whether or not the latter was associated with increased motor activity. They also reported that 5-hydroxyindole acetic acid excretion was increased with increased psychotic activity, and that catechol amine excretion was increased with increases in anxiety.

Kety prefaced his report by stating that it is possible that the relationship between psychosis and the biochemistry of the brain may not have been found yet, not because it isn't there, but because (*a*) concentration of a

chemical agent at its site of action may not parallel its concentration at the point where it is measured, and (*b*) psychiatric measures are more difficult and less accurate than biochemical measures. Of the compounds discussed by Kety in his report of studies with massive doses of possible precursors of serotonin, the two most active were tryptophan, which produced behavioral changes in 7 of 12 schizophrenics, and methionine, which affected 4 of 12 schizophrenics (not the same patients as those who reacted to tryptophan). He emphasized, however, that negative results with other possible precursors does not prove that they are not precursors because the concentration which penetrated the brain is not known.

Nicholas J. Giarman (Yale University, New Haven, Conn.) in discussing the latter two papers, described the different forms in which a compound may exist in the brain—precursor, free form, storage form (granular bound), active form (receptor bound), and metabolite. He noted that these different forms may make it meaningless to relate the effect of a psychoactive drug to its total concentration in the brain. He also reported the effect of tranquilizers, sedatives, depressants, and combinations of these drugs on the concentration in the brain of particle (bound) and supernatant (free) serotonin.

Eastern Psychological Association

Philadelphia, Pa., April 7–8, 1961

Barry, Herbert III. (Yale University, New Haven, Conn.) Effects of drugs on conflict in a shuttle alley with avoidance trained prior to approach.

Bindra, Dalbir, and Mendelson, Joseph. (McGill University, Montreal, Canada) Interaction of habit strength and drug effects.

Boff, Edward, and Heise, George A. (Hoffman-La Roche, Nutley, N.J.) Analysis of effects of graded doses of d-amphetamine on avoidance lever pressing rates and on general activity.

Boitano, John J. (Fordham University, New York, N.Y., and Institute of Living, Hartford, Conn.) The effects of chronic administration of chlorpromazine on frustrative behavior in monkeys.

Carlton, Peter L., and Horovitz, Z. P. (Squibb Institute for Medical Research, New Brunswick, N.J.) Behavioral and EEG effects of atropine and methyl atropine.

Carpenter, John A., Moore, Omar K., Snyder, Charles R., and Lisansky, Edith. (Yale University, New Haven, Conn.) The effect of alcohol on higher order problem solving.

DiMascio, Alberto. (Massachusetts Mental Health Center, Boston, Mass.) Stimulus generalization: its relation to discrimination, anxiety and perphenazine.

Engen, Trygg. (Brown University, Providence, R.I.) The influence of cross-adaptation on thresholds for aliphatic alcohols.

Ferster, C. B., Appel, J. B., and Hiss, R. (Indiana University, Medical Center, Indianapolis, Ind., Yale University, New Haven, Conn., and Kent State University, Kent, Ohio) Increased rates of responding after injections of amobarbital, pentobarbital, chlorpromazine, and d-amphetamine.

Geller, Irving. (Wyeth Laboratories, Philadelphia, Pa.) Contrasting effects of methaminodiazepoxide (Librium) and chlorpromazine on timing behavior in the rat.

Goldberger, Leo. (New York University, New York, N.Y.) Cognitive test performance under LSD, placebo, and isolation.

Linton, Harriet B., and Langs, Robert J. (New York University, New York, N.Y.) The reactions of placebo subjects in an LSD study.

Margules, David L. (University of Michigan, Ann Arbor, Mich.) Stimulus bound eating behavior and hunger controlled self-stimulation from the same locus in the hypothalamus.

Myers, Robert D. (Johns Hopkins University, Baltimore, Md.) Behavioral changes after intradiencephalic chemical stimulation of cats with chronically implanted cannulae.

Prescott, James W. (McGill University, Montreal, Canada) The effects of stimulant drugs and placebo upon the conditioned galvanic skin response.

Ray, Oakley S. (Veterans Administration Research Laboratories in Neuropsychiatry, Pittsburgh, Pa.) The effect of tranquilizers on positively and negatively motivated behavior studied simultaneously in rats.

Runyon, Richard P., and Turner, William J. (C. W. Post College of Long Island University, Greenvale, N.Y., and Central Islip State Hospital, Central Islip, N.Y.) Social structuring in psychopharmacological screening.

Schuette, Dorothy V. (University of Delaware, Newark, Del.) The effects of chlorpromazine upon the ear and the eighth cranial nerve.

Shurtleff, Donald, and Mostofsky, David. (Massachusetts Mental Health Center, Boston, Mass.) The effect of some phenothiazine derivatives on the discrimination of auditory flutter.

Midwestern Psychological Association

Chicago, Ill., May 5–6, 1961

Ansfield, Paul J. (Purdue University, Lafayette, Ind.), and Johnson, John I., Jr. (Marquette University, Milwaukee, Wis.) The Hebb-Williams maze as a measuring device for LSD effects in rats.

Cohen, Bertram D. (Lafayette Clinic, Detroit, Mich.), and Rosenbaum, Gerald. (Wayne State University, Detroit, Mich.) Simulation of schizophrenic performance with Sernyl, LSD–25, and amobarbital (Amytal) sodium: symbolic and sequential thinking.

Doyle, Gerald A., and Carlson, N. James. (Western Reserve University, Cleveland, Ohio) Effects of amphetamine and hunger on exploratory behavior and latent learning in rats.

Green, Phillip C., Pescor, Frank T., and Wikler, Abraham. (National Institute of Mental Health Addiction Research Center, Lexington, Ky.) Reinforcing effects of a synthetic opiate in conditioning of drug-seeking behavior in rats.

Haertzen, Charles A., Wolbach, Albert B., Jr., Wikler, Abraham, and Hill, Harris E. (National Institute of Mental Health

Addiction Research Center, Lexington, Ky.) Evaluating subjective effects of six drugs by means of an especially designed inventory.

Halasz, Michael F., and Hunt, Howard F. (University of Chicago, Chicago, Ill.) The effects of chlorpromazine on the extinction of inter-current avoidance and appetitive responses in the cat.

Harvey, John A., and Hunt, Howard F. (University of Chicago, Chicago, Ill.) Effect of meprobamate on an aversively controlled discrimination in normal rats and rats with lesions in the septal forebrain.

Gaito, John. (Lake Forest College, Lake Forest, Ill.) A biochemical conceptualization of learning and memory.

Palmer, Gail, Harlow, Harry F., and Waisman, Harry A. (University of Wisconsin, Madison, Wis.) Induced phenylpyruvic oligophrenia in infant monkeys.

Ray, Oakley S., and Marrazzi, Amedeo S. (Veterans Administration Research Laboratories in Neuropsychiatry, Pittsburgh, Pa.) Latency-measured conditioned emotional response procedures.

Russell, Roger W. (Indiana University, Bloomington, Ind.) Neurochemical lesions and behavior.

American Psychiatric Association

Chicago, Ill., May 8–12, 1961

Summaries of the papers and brief descriptions of the content of the roundtables are available in the publication entitled *Summaries of the Scientific Papers of the One Hundred and Seventeenth Annual Meeting,* which may be obtained from the APA at $3.00 per copy. Orders should be sent to the American Psychiatric Association, 1700 18th Street, N. W., Washington 9, D.C.

Aaron, Louis, Masserman, Jules H., and McAvoy, Thomas. (Northwestern University Medical School, Chicago, Ill.) Stimulation of the intact and injured brain.

Beckett, Peter G. S., Senf, Rita, and Frohman, Charles E. (Lafayette Clinic, Detroit, Mich.) Relations between energy transfer systems and the symptoms of schizophrenia.

Bennett, Jesse L., and Hamilton, L. Dean. (Veterans Administration Hospital, Salt Lake City, Utah.) Sequential use of psychic energizer drugs with chlorpromazine in chronic schizophrenia.

Bigelow, Newton, and Sainz, Anthony. (Marcy State Hospital, Marcy, N.Y.) Pitfalls in psychiatric research.

Bogoch, Samuel (Harvard Medical School, Boston, Mass.), Dusick, Karl T., and Conran, Peter. (Metropolitan State Hospital, Waltham, Mass.) Psychological and biochemical syntheses occurring during recovery from psychosis.

Brill, Henry, and Patton, Robert E. (New York State Department of Mental Hygiene, Albany, N.Y.) Clinical-statistical analysis of population changes in New York State mental hospitals since introduction of psychotropic drugs.

Busfield, Bernard Lawrence, Jr. (Massachusetts Mental Health Center), Schneller, Paul (Metropolitan State Hospital, Waltham, Mass.), and Capra, Dante V. (Westboro State Hospital, Westboro, Mass.) Depressive symptom or side effect? A comparative study of symptoms during pre-treatment and treatment periods of patients on three anti-depressant medications.

Epstein, Leon J., Morgan, Richard D., and Reynolds, A. B. (California Department of Mental Hygiene, Sacramento, Calif.) An approach to the question of the effects of ataraxic drugs on hospital release rates.

Gerard, Ralph W. (University of Michigan, Ann Arbor, Mich.) The nosology of schizophrenia.

Glick, Burton S., and Margolis, Reuben. (State University of New York, Downstate Medical Center, Brooklyn, N.Y.) A study of the influence of experimental design on clinical outcome in drug research.

Gottlieb, Jacques S., Luby, Elliot D., and Cohen, Bertram D. (Lafayette Clinic, Detroit, Mich.) Model psychoses and schizophrenia.

Hankoff, Leon D., Englehardt, David M., and Freedman, Norbert. (State University of New York, Downstate Medical Center, Brooklyn, N.Y.) Denial of illness in relation to differential drug response.

Lester, Eva P., Wittkower, Eric D., and Kalz, Frederick. (McGill University, Montreal, Canada) Phrenotropic agents in psychosomatic disorders (skin).

Molling, Peter A., Lockner, Arthur W., Jr., Eisenberg, Leon (Johns Hopkins Hospital, Baltimore, Md.), and Robert J. Sauls. (Boys' Village, Cheltenham, Md.) The impact of placebo and of perphenazine in committed delinquent boys.

Peterson, Donald B., and Olson, Gordon W. (Anoka State Hospital, Anoka, Minn.) Intermittent chemotherapy for chronic psychiatric inpatients.

Sainato, Helen K., and Waldrop, Francis N. (St. Elizabeths Hospital, Washington, D.C.) An investigation of the interaction between drug treatment and nursing care in a mental hospital setting.

Tanner, Henry. (Veterans Administration Hospital, Northampton, Mass.), Weinberger, Julius, and Blumenthal, Irving J. (Veterans Administration Hospital, Northport, N.Y.) Long-term progress of hospitalized schizophrenic patients on ataractic drugs.

Wilkens, Bernard, Malitz, Sidney, and Esecover, Harold. (New York State Psychiatric Institute, New York, N.Y.) Clinical observations of simultaneous hallucinogen administration in identical twins.

Roundtable meeting on "Non-drug Influences in Psychopharmacological Research," chaired by David M. Englehardt of the State University of New York, Downstate Medical Center, Brooklyn, N.Y. Participants: H. Azima (McGill University, Montreal, Canada), Henry K. Beecher (Harvard Medical School, Boston, Mass.), Leon J. Epstein (State of California Department of Mental Hygiene, Sacramento, Calif.), Paul E. Feldman (Topeka State Hospital, Topeka, Kans.), Max Fink (Hillside Hospital, Glen Oaks, N.Y.), and Leon D. Hankoff (State University of New York, Downstate Medical Center, Brooklyn, N.Y.).

American Society of Medical Psychiatry

Chicago, Ill., May 7, 1961

Ayd, Frank, Jr. (Franklin Square Hospital, Baltimore, Md.) A critical appraisal of Librium.

Brunner-Orme, Martha. (Westwood, Mass.) The evaluation of Temposil in the treatment of alcoholics.

Dussik, Karl T., Grunberg, Emile, McLaughlin, William, and White, Joel J. (Metropolitan State Hospital, Waltham, Mass.) Glucagon-induced insulin coma and the synergistic use of the newer drugs.

Karliner, William (Scarsdale, N.Y.), and Padula, Louis J. Further clinical studies of Indoklon convulsive treatments.

Karliner, William (Scarsdale, N.Y.), and Padula, Louis J. Fate of Indoklon in the body. (Read by title.)

LaVerne, Albert A. (New York, N.Y.) Serum normalizing therapy.

Lesse, Stanley. (Neurological Institute of New York, New York, N.Y.) Psychotherapy combined with anti-depressant drugs—a study of 150 cases.

Liberson, W. T., and Kafka, A. (Veterans Administration Hospital, Hines, Ill.) Effects of Librium on fixation in rats.

Moriarity, John D. (Los Angeles, Calif.) and Mebane, John C. (Hollywood, Calif.) Double blind study of methominodiazepoxide (Librium) in office practice.

Murray, Neville. (Murray Clinic, San Antonio, Tex.) Covert effects of Librium therapy.

Robie, Theodore R. (Montclair, N.J.) Etryptamine—a new antidepressant chemical for depression.

Rothman, Theodore (Beverly Hills, Calif.), Grayson, Harry M. (Veterans Administration Center, Los Angeles, Calif.), and Ferguson, James. (Santa Monica, Calif.) Affective, psychomotor and autonomic changes associated with isocarboxazid (Marplan) and imipramine (Tofranil) in the treatment of depressive syndrome.

Tucker, Walter I. (Lahey Clinic, Boston, Mass.) Progesterone treatment in post-partum and schizo-affective reactions.

International Conference on EEG and Human Psychopharmacology

Montreal, Canada, June 1961

The International Conference on EEG and Human Psychopharmacology, held in Montreal in June 1961 in conjunction with the World Congress of Psychiatry, provided a forum for discussion of essentially two main questions: (*a*) Do consistent electrographic patterns occur in man following acute and chronic administration of psychopharmacological agents, and if they do, what are the most effective techniques for demonstrating them? (*b*) What is the significance of the EEG patterns for the behavioral changes which such agents induce in psychiatric patients? This meeting was organized following informal meetings of the participants at the Collegium Internationale Neuro-Psychopharmacologicum in Basel, Switzerland, in 1960.

Psychopharmacologists, electroencephalographers, and psychiatrists from Europe, North America, and Australia exchanged observations, compared and evaluated techniques and methods of analysis, and examined the significance of current hypotheses relating brain function to behavior. The participants included K. Andermann (Australia), D. Bente (Germany), J. Cahn (France), F. Hajnesk (Yugoslavia), H. Lechner (Austria), J. Schneider (France), G. Ulett (U.S.A.), G. Verdeaux (France), and H. Jasper (Canada).

The general discussions as well as the formal presentations were simultaneously translated into French, English, and German.

Consistent patterns of changes in frequency spectrum, in rhythms, in response to eye-opening, and in hyperventilation were reported for both chronic oral and acute intravenous administration of a variety of active psychotropic agents, including phenothiazine derivatives, imipramine, and newer anticholinergic antidepressives. While these patterns were demonstrable on rapid visual analysis of records, the participants emphasized the importance of quantitative frequency analyses and detailed, systematic measurements of the patterns. The applicability of electronic frequency analyses to these problems was demonstrated.

The panelists showed considerable agreement that changes in EEG patterns were most prominent with effective psychotropic agents, and that EEG pattern changes were concomitant with, and often preceded, behavioral change. The prominence of the EEG change in the temporal electrodes led to a discussion of anatomical substrates for the behavioral effects of drugs. Other discussions centered about the neurophysiologic-adaptive model of drug action.

The significance of activation procedures, such as Metrazol, flicker, and barbiturates, was also discussed.

The conference was chaired by Max Fink of Hillside Hospital, Glen Oaks, N.Y. He, H. C. Denber, and S. Merlis of New York organized this meeting, the first in a series of conferences on the role of altered brain function in behavior and the applicability of findings from that area of research to the screening of new drugs and the understanding of drug therapy in psychiatry. A second meeting has been arranged by F. Flügel and Deiter Bente of Erlangen, and will be held in Nuremberg, Germany, in conjunction with the Deutsche Arbeitsgemeinschaft für Neuropsychopharmacologie on September 1–3, 1961.

The proceedings of the Montreal conference will be edited and submitted for publication following the Nuremberg meeting. Further information about the proceedings may be obtained from Dr. Fink.

Publications and Other Informational Materials

In this section of the Bulletin are listed various materials available from the Scientific Information Unit of the PSC and a few other miscellaneous publications. The Bulletin does not try to list all new publications, but only those, e.g., Government reports and foreign publications, that might not ordinarily come to the attention of psychopharmacologists. Please write to the Bulletin if you know of any publications that you think should be listed.

MATERIALS AVAILABLE FROM THE SCIENTIFIC INFORMATION UNIT OF THE PSYCHOPHARMACOLOGY SERVICE CENTER

Psychopharmacology Service Center of the National Institute of Mental Health. December, 1960.

This little pamphlet describes the activities of the PSC, the research program and how grants are awarded, and the services which the Center offers to investigators working in this field. A copy has already been mailed to all recipients of the *Bulletin*. The Center has additional copies and will be glad to send them on request.

Psychopharmaca, A Bibliography of Psychopharmacology, 1952–1957. Compiled by Anne E. Caldwell. Washington, D.C. Government Printing Office, 1958.

This bibliography was out of print for several months. It has now been reprinted and the Center has copies for distribution.

References on Tranquilizers and the Electroencephalogram. February 1961.

445 references concerned with the effects of tranquilizers on the electroencephalogram. Not annotated.

Reference List on Prothipendyl Hydrochloride (Timovan, Dominal) February 1961.

25 references. Not annotated.

Tables Summarizing Information on Side Effects and Toxicity of Newer Psychopharmacological Agents. Prepared by Reuben M. Cares, M.D., Director of Clinical Laboratories, Kings Park State Hospital, and Charles Buckman, M.D., Director, Kings Park State Hospital, Kings Park, N.Y. Presented as part of a paper entitled "A Survey of Side Effects or Toxicity of Newer Psychopharmacologic Agents" at the Fifth Annual Meeting of the Eastern Psychiatric Research Association, New York City, November 4, 1960.

The information in these tables is based on a literature survey of journals from 1956 to 1960.

OTHER PUBLICATIONS

Drug Enhancement of Performance, by Nicholas Plotnikoff, Lucy Birzis, Chozo Mitoma, Leon Otis, Bernard Weiss, and Victor Laties. (SRI Project No. SU–3024; prepared under contract Nonr–2993(00) for the Office of Naval Research of the U.S. Department of the Navy). Menlo Park, Calif.: Stanford Research Institute, 1960.

A limited number of copies are available on a first-come, first-serve basis. Write to Dr. Nicholas Plotnikoff, Stanford Research Institute, Menlo Park, Calif.

This report surveys the published literature on the pharmacological, neurophysiological, biochemical, and psychological or behavioral effects of stimulant and antidepressive drugs in animals and in normal human subjects. Specialists in each of these four scientific disciplines have reviewed the literature, summarized present research needs, and recommended directions for future research. The drugs covered include the amphetamines and other CNS stimulants, MAO inhibitors and other antidepressives, and hallucinogenic stimulants.

Transactions of the Fifth Research Conference on Cooperative Chemotherapy Studies in Psychiatry and Research Approaches to Mental Illness, Vol. V. Washington, D.C.: Veterans Administration, 1960.

To obtain copies write to Mr. Clyde J. Lindley, Executive Secretary of the VA Cooperative Chemotherapy Studies in Psychiatry, Psychiatry and Neurology Service, Veterans Administration, Washington 25, D.C. A few copies of earlier volumes are still available; they, too, may be obtained from Mr. Lindley.

Like the first four volumes reporting proceedings of the Veterans Administration's annual conferences on the Cooperative Chemotherapy Studies in Psychiatry, this one contains preliminary reports of findings from cooperative studies conducted during the year preceding the conference, progress reports on projects under way, and reports on a number of individual research projects carried out in VA installations. The first four volumes, however, were devoted entirely to research relevant to chemotherapy; Volume V, as its title indicates, is broader in scope.

The cooperative studies which were discussed investigated (*a*) the response of chronic withdrawn schizophrenics to combinations of drugs (chlorpromazine combined with dextro-amphetamine, isocarboxazid, trifluoperazine, imipramine, or placebo; (*b*) the effects of

tranquilizers (chlorpromazine, meprobamate, phenobarbital, or placebo) on anxiety and hostility in outpatients in psychotherapy; and (*c*) the comparative effectiveness of chlorpromazine, chlorprothixene, reserpine, fluphenazine, thioridazine, and trifluprom azine in the treatment of newly admitted schizophrenic patients.

The subject matter of the individual research papers ranges from investigations of urinary excretion patterns and drug metabolism in psychiatric patients, through clinical and methodological studies, to presentation of a psychological rationale for the effects of antidepressive drugs.

The remaining sessions of the conference were devoted to symposia on broad approaches to mental illness, significant approaches to the study of depression, use of control substances in drug studies, prognostic indicators and measures of change in schizophrenia, biological correlates of mental disturbance, research on the aged psychiatric patient, and modern concepts and techniques in reseach design.

Appendixes to the transactions contain a statistical supplement to reports on the cooperative study of combined drug therapy in chronic schizophrenics and the final protocol for the cooperative study of the comparative effects of several tranquilizers in the treatment of newly admitted schizophrenics. An author index and a subject index are also included.

Einführung in die Pharmakopsychologie, by Herbert Lippert. Bern and Stuttgart: Hans Huber, 1959. (32 DM; price in the U.S., $8.00.)

Following an introductory chapter on the concepts and history of "pharmacopsychology," the author reviews the pharmacopsychology of instinct, feelings and mood, perception and imagination, thought and will, action or activity, expression, consciousness, development, culture, "pharmacocharacterology," general methods of pharmacopsychology, and the chemical structure and psychic effects of drugs.

In a review published in the November 1960 issue of *Contemporary Psychology* (Vol. V., No. 11, pp. 357–358), Hans-Lukas Teuber observes that this book probably is the first attempt at monographic presentation of the systematic study of the use of drugs to modify behavior. He comments that Lippert "has set himself the task of surveying the vast literature of psychopharmacology with heavy emphasis on drugs that disturb behavior—alcohol, opiates, hallucinogens—and with duly critical comments on those recent 'tranquilizing' drugs that are reputed to alleviate misbehavior . . . . His methods are descriptive, phenomenological, and literary. He covers nearly 1,700 references (only half of them German, the rest mostly English). His text gives a panorama of introspective accounts, from Baudelaire's experience with hashish to current reports of mescaline visions or of mood changes under the influence of tranquilizers. . . . Lippert's sensitivity to the social factors shows in his discussions of addiction, or of the use of drugs in the procedures for interrogation and 'brain-washing.' Yet his exclusion of physiologic questions may be at the root of a difficulty which pervades the book and which he deplores in its closing section: that the studies he reviews fail to fit together, that there is no rational approach to the riddle of how chemical substances can affect the mind. We may never find out, says Lippert, unless we know what mind (*Seele*) really is."

Forthcoming Meetings

Listed here are a few forthcoming meetings in the field of psychopharmacology. Conventions and meetings of large professional and scientific societies are not included because announcements of these meetings are generally available in other publications. Please write to the *Bulletin* if you know of meetings that might be listed.

International Symposium on the Influence of Psychotropic Drugs on Higher Nervous Activity, October 31–November 3, 1961, Prague, Czechoslovakia, under sponsorship of the Society for the Study of Higher Nervous Activity, a section of the Czechoslovak Medical Society. The official languages are Russian, Czech, and English. The program will stress experimental methodology and problems related to drug evaluation in both clinical and experimental situations. Physiological, behavioristic, and experimental approaches will be covered. For further information, write to Dr. O. Vinař, Bohnice 95, Prague 8, Czechoslovakia.

Symposium on the Psychophysiology, Neuropharmacology, and Biochemistry of the Audiogenic Seizure, November 1961, Gif-sur-Yvette (Seine-et-Oise), France, under sponsorship of the Centre National de la Recherche Scientifique. Further information may be obtained from Professor R.-G. Busnel, Directeur du Laboratoire de Physiologie Acoustique, Centre National de Recherchez Zootechniques, Jouy-en-Josas (Seine-et-Oise), France.

International conference on the role of altered brain function in behavior, to be held in conjunction with the Deutsche Arbeitsgemeinschaft für Neuropsychopharmakologie, September 1–3, 1961, Nuremberg, Germany. This is the second in a series of conferences on this topic. (A report on the first one, the International Conference on EEG and Human Psychopharmacology, appears on page 34 of this issue of the *Bulletin.*) For further information write to Professor F. Flügel, Universitats-Nervenklinik, Erlangen, Germany, or to Dr. Max Fink, Hillside Hospital, Glen Oaks, N.Y.

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